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	<i>DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR</i>		
<input type="checkbox"/>	L1	oxide or glycine or gaba or serotonin or dopamine or epinephrine or norepinephrine or nor-epinephrine	1731602
<input type="checkbox"/>	L2	inhibit\$ or antagon\$ or block\$ or inactiv\$ or modulat\$	4765406
<input type="checkbox"/>	L3	L2 near5 l1	63251
<input type="checkbox"/>	L4	L3 same bladder	171
<input type="checkbox"/>	L5	L3 same lumen	95
<input type="checkbox"/>	L6	L3 same intravesically	3
<input type="checkbox"/>	L7	L3 same intravesi\$	32
<input type="checkbox"/>	L8	(l1.clm. and l2.clm.) and inconten\$.clm.	0
<input type="checkbox"/>	L9	(method or process).clm. same (incontinen\$ or urologic\$ or hyperreflexia or detrusor or bladder or urinary or urothelium or lumen).clm.	14727
<input type="checkbox"/>	L10	(method or process).clm. same (incontinen\$ or urologic\$ or hyperreflexia or detrusor or bladder or urinary or urothelium).clm.	7444
<input type="checkbox"/>	L11	l9 and l3.clm.	204
<input type="checkbox"/>	L12	L11 and (lumen or intravesic\$ or topical\$).clm.	64
<input type="checkbox"/>	L13	intravesical\$	2272
<input type="checkbox"/>	L14	L13 same \$toxin	25

END OF SEARCH HISTORY

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SCHMIDT RA, 1988, V7, P585, NEUROUROL URODYNAM  
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10/9/7 (Item 7 from file: 34)

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

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08140537 Genuine Article#: 250YE Number of References: 54

Title: Intravesical instillations of capsaicin in urology: from  
pharmacological principles to therapeutic applications.

Author(s): deSeze M (REPRINT) ; Wiart L; Ferriere JM; deSeze MP; Joseph PA;  
Barat M

Corporate Source: HOP PELLEGRIN, SERV REEDUC FONCT NEUROL/F-33076

BORDEAUX//FRANCE/ (REPRINT); CTR REEDUC FONCT TOUR

GASSIES, /BRUGGE//BELGIUM/; HOP PELLEGRIN, SERV CHIRURG UROL/F-33076

BORDEAUX//FRANCE/

Journal: PROGRES EN UROLOGIE, 1999, V9, N4 (SEP), P615-632

ISSN: 1166-7087 Publication date: 19990900

Publisher: PROGRES EN UROLOGIE, 76 RUE DE LA POMPE, 75016 PARIS, FRANCE

Language: French Document Type: REVIEW

Geographic Location: FRANCE; BELGIUM

Subfile: CC CLIN--Current Contents, Clinical Medicine;

Journal Subject Category: UROLOGY & NEPHROLOGY

Abstract: Capsaicin is a specific neurotoxin for type C nonmyelinated vesical afferent fibres involved in the transmission of nociceptive stimuli and reorganization of voiding reflexes in disease. The presence of afferents sensitive to vanilloid substances in the human bladder suggests the potential value of intravesical instillations of capsaicin in patients with symptoms of bladder hypersensitivity or bladder hyperactivity. Ten clinical trials document the efficacy and safety of vesical instillation capsaicin in 200 patients with neurological or non-neurological lower urinary tract symptoms. The objective of this review is to analyse these various publications in order to define the indications and practical conditions of intravesical instillation of capsaicin. The value of intravesical capsaicin in neurogenic bladder hyperactivity has been clearly demonstrated. In non-neurological indications, the diversity of instillation protocols and the heterogeneity of the evaluation parameters complicate analysis of the results. Repeated low-dose capsaicin appears to be useful in bladder hyperactivity, but the value of capsaicin is uncertain in idiopathic detrusor instability. Transient adverse effects are almost systematically observed after intravesical capsaicin. The short-term and medium-term local histological safety appears to be satisfactory, but needs to be documented in the long-term.

Descriptors--Author Keywords: capsaicin ; neurogenic bladder ; bladder hyperactivity ; bladder pain

Identifiers--KeyWord Plus(R): PRIMARY SENSORY NEURONS; LOWER URINARY-TRACT; DETRUSOR HYPERREFLEXIA; BLADDER DYSFUNCTION; MICTURITION REFLEX; SUBSTANCE-P; RAT; RESINIFERATOXIN; DESENSITIZATION; PAIN

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10/9/8 (Item 8 from file: 155)  
 DIALOG(R) File 155:MEDLINE(R)  
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12637259 PMID: 10555213

[Intravesical instillations of capsaicin in urology: from pharmacological principles to therapeutic applications]

Instillations intravesicales de capsaïcine en urologie. Des principes pharmacologiques aux applications therapeutiques.

de Seze M; Wiart L; Ferriere J M; de Seze M P; Joseph P A; Barat M  
Service de Reeducation Fonctionnelle Neurologique, Hopital Pellegrin  
Tastet-Girard, Bordeaux, France.

Progres en urologie - journal de l'Association francaise d'urologie et de  
la Societe francaise d'urologie (FRANCE) Sep 1999, 9 (4) p615-32,  
ISSN 1166-7087 Journal Code: 9307844

Publishing Model Print

Document type: Journal Article; Review; Review, Tutorial ; English  
Abstract

Languages: FRENCH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS

Capsaicin is a specific neurotoxin for type C nonmyelinated vesical afferent fibres involved in the transmission of nociceptive stimuli and reorganization of voiding reflexes in disease. The presence of afferents sensitive to vanilloid substances in the human bladder suggests the potential value of intravesical instillations of capsaicin in patients with symptoms of bladder hypersensitivity or bladder hyperactivity. Ten clinical trials document the efficacy and safety of vesical instillation of capsaicin in 200 patients with neurological or non-neurological lower urinary tract symptoms. The objective of this review is to analyse these various publications in order to define the indications and practical conditions of intravesical instillation of capsaicin. The value of intravesical capsaicin in neurogenic bladder hyperactivity has been clearly demonstrated. In non-neurological indications, the diversity of instillation protocols and the heterogeneity of the evaluation parameters complicate analysis of the results. Repeated low-dose capsaicin appears to be useful in bladder hyperactivity, but the value of capsaicin is uncertain in idiopathic detrusor instability. Transient adverse effects are almost systematically observed after intravesical capsaicin. The short-term and medium-term local histological safety appears to be satisfactory, but needs to be documented in the long-term. (54 Refs.)

Tags: Comparative Study; Female; Male; Research Support, Non-U.S. Gov't

Descriptors: \*Bladder Diseases--drug therapy--DT; \*Capsaicin  
--administration and dosage--AD; \*Urinary Incontinence--drug therapy--DT;  
Administration, Intravesical; Adolescent; Adult; Aged; Animals; Bladder  
--drug effects--DE; Bladder--innervation--IR; Bladder Diseases  
--physiopathology--PP; Bladder, Neurogenic--drug therapy--DT; Bladder,  
Neurogenic--physiopathology--PP; Capsaicin--pharmacology--PD; Cats;  
Clinical Trials; Data Interpretation, Statistical; Drug Tolerance;  
Follow-Up Studies; Humans; Middle Aged; Pain--etiology--ET; Rats; Time  
Factors; Urinary Incontinence--physiopathology--PP; Urodynamics

CAS Registry No.: 404-86-4 (Capsaicin)

Record Date Created: 19991130

Record Date Completed: 19991130

10/9/9 (Item 9 from file: 155)

DIALOG(R) File 155:MEDLINE(R)

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11033827 PMID: 7609147

Urodynamic effects of intravesical resiniferatoxin and capsaicin in conscious rats with and without outflow obstruction.

Ishizuka O; Mattiasson A; Andersson K E

Department of Urology, Lund University Hospital, Sweden.

Journal of urology (UNITED STATES) Aug 1995, 154 (2 Pt 1) p611-6,

ISSN 0022-5347 Journal Code: 0376374

Publishing Model Print

Document type: Journal Article



Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: AIM; INDEX MEDICUS

PURPOSE: The urodynamic effects of intravesical resiniferatoxin and capsaicin were investigated in rats. MATERIALS AND METHODS: Continuous cystometry was performed in conscious, female Sprague-Dawley rats with and without outflow obstruction. RESULTS: Intravesical instillation of resiniferatoxin facilitated micturition. The potency of the drug was approximately 1,000 times higher than that of capsaicin. Repeated instillations of resiniferatoxin for 6 consecutive days caused desensitization to resiniferatoxin. This was not found with repeated instillations of capsaicin. Capsaicin was also effective in rats with bladder hypertrophy, while resiniferatoxin was not. CONCLUSIONS: The findings suggest that resiniferatoxin can induce desensitization of vanilloid receptor-mediated release of tachykinins in the rat urinary bladder and that intravesical resiniferatoxin would be an interesting alternative to intravesical capsaicin in the treatment of selected cases of bladder hypersensitivity/hyperactivity.

Tags: Female; Research Support, Non-U.S. Gov't

Descriptors: \*Capsaicin--pharmacology--PD; \*Diterpenes--pharmacology--PD; \*Neurotoxins--pharmacology--PD; \*Urethral Obstruction--physiopathology--PP; \*Urodynamics--drug effects--DE; Administration, Intravesical; Animals; Benzamides--pharmacology--PD; Bladder --drug effects--DE; Bladder --physiopathology--PP; Consciousness; Diterpenes --antagonists and inhibitors--AI; Neurotoxins --antagonists and inhibitors--AI; Piperidines --pharmacology--PD; Rats; Rats, Sprague-Dawley; Receptors, Tachykinin --antagonists and inhibitors--AI

CAS Registry No.: 0 (Benzamides); 0 (Diterpenes); 0 (Neurotoxins); 0 (Piperidines); 0 (Receptors, Tachykinin); 142001-63-6 (SR 48968); 404-86-4 (Capsaicin); 57444-62-9 (resiniferatoxin)

Record Date Created: 19950814

Record Date Completed: 19950814

10/9/10 (Item 10 from file: 156)

DIALOG(R) File 156:ToxFile

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3372018 NLM Doc No: 10555213

[Intravesical instillations of capsaicin in urology: from pharmacological principles to therapeutic applications]

Instillations intravesicales de capsaicine en urologie. Des principes pharmacologiques aux applications therapeutiques.

de Seze M; Wiart L; Ferriere J M; de Seze M P; Joseph P A; Barat M

Service de Reeducation Fonctionnelle Neurologique; Hopital Pellegrin Tastet-Girard, Bordeaux, France.

Journal Name: Progres en urologie - journal de l'Association francaise d'urologie et de la Societe francaise d'urologie (FRANCE) Pub. Year: Sep 1999 9 (4) p615-32, ISSN: 1166-7087 Journal Code: 9307844

Publishing Model Print

Document type: Journal Article; Review; Review, Tutorial ; English Abstract

Languages: FRENCH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: Toxbib ; INDEX MEDICUS

Capsaicin is a specific neurotoxin for type C nonmyelinated vesical afferent fibres involved in the transmission of nociceptive stimuli and reorganization of voiding reflexes in disease. The presence of afferents sensitive to vanilloid substances in the human bladder suggests the

potential value of intravesical instillations of capsaicin in patients with symptoms of bladder hypersensitivity or bladder hyperactivity. Ten clinical trials document the efficacy and safety of vesical instillation of capsaicin in 200 patients with neurological or non-neurological lower urinary tract symptoms. The objective of this review is to analyse these various publications in order to define the indications and practical conditions of intravesical instillation of capsaicin. The value of intravesical capsaicin in neurogenic bladder hyperactivity has been clearly demonstrated. In non-neurological indications, the diversity of instillation protocols and the heterogeneity of the evaluation parameters complicate analysis of the results. Repeated low-dose capsaicin appears to be useful in bladder hyperactivity, but the value of capsaicin is uncertain in idiopathic detrusor instability. Transient adverse effects are almost systematically observed after intravesical capsaicin. The short-term and medium-term local histological safety appears to be satisfactory, but needs to be documented in the long-term. (54 Refs.)

Tags: Comparative Study; Female; Male; Research Support, Non-U.S. Gov't  
Descriptors: \*Bladder Diseases--drug therapy--DT; \*Capsaicin  
--administration and dosage--AD; \*Urinary Incontinence--drug therapy--DT;  
Administration, Intravesical; Adolescent; Adult; Aged; Animals; Bladder  
--drug effects--DE; Bladder--innervation--IR; Bladder Diseases  
--physiopathology--PP; Bladder, Neurogenic--drug therapy--DT; Bladder,  
Neurogenic--physiopathology--PP; Capsaicin--pharmacology--PD; Cats;  
Clinical Trials; Data Interpretation, Statistical; Drug Tolerance;  
Follow-Up Studies; Humans; Middle Aged; Pain--etiology--ET; Rats; Time  
Factors; Urinary Incontinence--physiopathology--PP; Urodynamics

CAS Registry No.: 404-86-4 (Capsaicin)

Record Date Created: 19991130

Record Date Completed: 19991130

10/9/11 (Item 11 from file: 156)  
DIALOG(R) File 156:ToxFile  
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3140234 NLM Doc No: 7609147

Urodynamic effects of intravesical resiniferatoxin and capsaicin in conscious rats with and without outflow obstruction.

Ishizuka O; Mattiasson A; Andersson K E

Department of Urology, Lund University Hospital, Sweden.

Journal Name: Journal of urology (UNITED STATES) Pub. Year: Aug 1995  
154 (2 Pt 1) p611-6, ISSN: 0022-5347 Journal Code: 0376374

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: Toxbib ; AIM; INDEX MEDICUS

PURPOSE: The urodynamic effects of intravesical resiniferatoxin and capsaicin were investigated in rats. MATERIALS AND METHODS: Continuous cystometry was performed in conscious, female Sprague-Dawley rats with and without outflow obstruction. RESULTS: Intravesical instillation of resiniferatoxin facilitated micturition. The potency of the drug was approximately 1,000 times higher than that of capsaicin. Repeated instillations of resiniferatoxin for 6 consecutive days caused desensitization to resiniferatoxin. This was not found with repeated instillations of capsaicin. Capsaicin was also effective in rats with bladder hypertrophy, while resiniferatoxin was not. CONCLUSIONS: The findings suggest that resiniferatoxin can induce desensitization of vanilloid receptor-mediated release of tachykinins in the rat urinary bladder and that intravesical resiniferatoxin would be an interesting

alternative to intravesical capsaicin in the treatment of selected cases of bladder hypersensitivity/hyperactivity.

Tags: Female; Research Support, Non-U.S. Gov't

Descriptors: \*Capsaicin--pharmacology--PD; \*Diterpenes--pharmacology--PD; \*Neurotoxins--pharmacology--PD; \*Urethral Obstruction--physiopathology--PP; \*Urodynamics--drug effects--DE; Administration, Intravesical; Animals; Benzamides--pharmacology--PD; Bladder --drug effects--DE; Bladder --physiopathology--PP; Consciousness; Diterpenes --antagonists and inhibitors--AI; Neurotoxins --antagonists and inhibitors--AI; Piperidines --pharmacology--PD; Rats; Rats, Sprague-Dawley; Receptors, Tachykinin --antagonists and inhibitors--AI

CAS Registry No.: 0 (Benzamides); 0 (Diterpenes); 0 (Neurotoxins); 0 (Piperidines); 0 (Receptors, Tachykinin); 142001-63-6 (SR 48968); 404-86-4 (Capsaicin); 57444-62-9 (resiniferatoxin)

Record Date Created: 19950814

Record Date Completed: 19950814

10/9/12 (Item 12 from file: 144)

DIALOG(R)File 144:Pascal

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15049496 PASCAL No.: 01-0207261

The role of bladder afferent pathways in bladder hyperactivity induced by the intravesical administration of nerve growth factor

CHUANG Yao-Chi; FRASER Matthew O; YONGBEI YU; CHANCELLOR Michael B; DE GROAT William C; YOSHIMURA Naoki

Departments of Pharmacology and Urology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, United States; Division of Urology, Chang Gung Memorial Hospital, Kaohsiung, Taiwan; Department of Urology, National Yang Ming University, School of Medicine, Taipei, Taiwan

Journal: The Journal of urology, 2001, 165 (3) 975-979

ISSN: 0022-5347 CODEN: JOURAA Availability: INIST-2081; 354000098721450620

No. of Refs.: 20 ref.

Document Type: P (Serial) ; A (Analytic)

Country of Publication: United States

Language: English

Purpose: Interstitial cystitis, a chronic disease of the bladder, is characterized by urinary frequency, urgency and suprapubic pain. Nerve growth factor is a substance that may sensitize afferent nerves and induce bladder hyperactivity. It is often increased in the urine of patients with interstitial cystitis. We evaluated the role of AS and C fiber afferents in the type of bladder hyperactivity induced by the intravesical administration of nerve growth factor. Materials and Methods: A total of 22 Wistar and 8 Sprague-Dawley adult female rats were anesthetized with 1.2 gm./kg. urethane given subcutaneously. A transurethral catheter was inserted into the bladder. Some animals were pretreated with 125 mg./kg. capsaicin injected subcutaneously 4 days before nerve growth factor administration. Cystometry was performed by slowly filling the bladder at a rate of 0.04 ml. per minute for 15 minutes with a volume of up to 0.6 ml. Parameters measured included volume threshold and pressure threshold for inducing the micturition reflex, compliance, bladder contraction amplitude, number of contractions and the inter-contraction interval. Nerve growth factor (0.5 ml. of 20 µg./ml. in 10% dimethyl sulfoxide) or a vehicle solution (0.5 ml. of 10% dimethyl sulfoxide) was infused into the bladder through a transurethral catheter and retained for 1 hour. Results: In Wistar rats nerve growth factor increased the mean number of contractions by 111% versus controls (5.7 versus 2.7,  $p < 0.05$ ), and decreased the mean volume threshold by 41% (0.244 versus 0.412 ml.,  $p < 0.05$ ). This effect of nerve growth factor was not detected in Sprague-Dawley rats. Capsaicin

pretreatment increased the volume threshold by 59% but did not change nerve growth factor induced bladder hyperactivity. Conclusions: The intravesical application of nerve growth factor acutely induced bladder hyperactivity in Wistar but not in Sprague-Dawley rats. Because the C fiber afferent neurotoxin capsaicin did not change the effect of nerve growth factor, we believe that AS afferent neurons have a major role in nerve growth factor induced bladder hyperactivity.

English Descriptors: Urinary incontinence; Hyperactivity; Experimental study; Animal model; Animal; Rat; Cystitis; Interstitial; Nerve growth factor; Neurophysiology; Nerve fiber C; Nerve fiber A; Evaluation  
Broad Descriptors: Rodentia; Mammalia; Vertebrata; Urinary system disease; Urinary tract disease; Bladder disease; Voiding dysfunction; Rodentia; Mammalia; Vertebrata; Appareil urinaire pathologie; Voie urinaire pathologie; Vessie pathologie; Trouble miction; Rodentia; Mammalia; Vertebrata; Aparato urinario patologia; Via urinaria patologia; Vejiga patologia; Trastorno miccion

French Descriptors: Incontinence urinaire; Hyperactivite; Etude experimentale; Modele animal; Animal; Rat; Cystite; Interstitiel; Facteur croissance nerf; Neurophysiologie; Fibre nerveuse C; Fibre nerveuse A; Evaluation; Nerf afferent

Classification Codes: 002B14E02; 002A18  
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10/9/13 (Item 13 from file: 73)  
DIALOG(R) File 73:EMBASE  
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11038067 EMBASE No: 2001069056

The role of bladder afferent pathways in bladder hyperactivity induced by the intravesical administration of nerve growth factor

Chuang Y.-C.; Fraser M.O.; Yu Y.; Chancellor M.B.; De Groat W.C.; Yoshimura N.

Y.-C. Chuang, Division of Urology, Chang Gung Memorial Hospital, 123 Ta-pei Road, Niao-Sung Hsiang, Kaohsiung Taiwan

Journal of Urology ( J. UROL. ) (United States) 2001, 165/3 (975-979)

CODEN: JOURA ISSN: 0022-5347

DOCUMENT TYPE: Journal ; Article

LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

NUMBER OF REFERENCES: 20

Purpose: Interstitial cystitis, a chronic disease of the bladder, is characterized by urinary frequency, urgency and suprapubic pain. Nerve growth factor is a substance that may sensitize afferent nerves and induce bladder hyperactivity. It is often increased in the urine of patients with interstitial cystitis. We evaluated the role of Adelta and C fiber afferents in the type of bladder hyperactivity induced by the intravesical administration of nerve growth factor. Materials and Methods: A total of 22 Wistar and 8 Sprague-Dawley adult female rats were anesthetized with 1.2 gm./kg. urethane given subcutaneously. A transurethral catheter was inserted into the bladder. Some animals were pretreated with 125 mg./kg. capsaicin injected subcutaneously 4 days before nerve growth factor administration. Cystometry was performed by slowly filling the bladder at a rate of 0.04 ml. per minute for 15 minutes with a volume of up to 0.6 ml. Parameters measured included volume threshold and pressure threshold for inducing the micturition reflex, compliance, bladder contraction amplitude, number of contractions and the inter-contraction interval. Nerve growth

DOCUMENT-IDENTIFIER: US 6713479 B2

TITLE: Piperidine-piperazine ligands for neurotransmitter receptors

## CLAIMS:

39. A method of modulating the activity of a dopamine, serotonin, or norepinephrine receptor or transporter in a mammal, comprising the step of: administering to a mammal a therapeutically effective amount of a compound of claim 1.

49. The method of claim 39, wherein said compound is administered topically.

54. A method of modulating the activity of a serotonin receptor or transporter in a mammal, comprising the step of: administering to a mammal a therapeutically effective amount of a compound of claim 1.

64. The method of claim 54, wherein said compound is administered topically.


69. A method of treating a mammal suffering from addiction, anxiety, depression, sexual dysfunction, hypertension, migraine, Alzheimer's disease, obesity, emesis, psychosis, analgesia, schizophrenia, Parkinson's disease, restless leg syndrome, sleeping disorders, attention deficit hyperactivity disorder, irritable bowel syndrome, premature ejaculation, menstrual dysphoria syndrome, urinary incontinence, inflammatory pain, neuropathic pain, Lesche-Nyhane disease, Wilson's disease, or Tourette's syndrome, comprising the step of: administering to a mammal a therapeutically effective amount of a compound of claim 1.

4

79. The method of claim 69, wherein said compound is administered topically.

Entry 50 of 64

File: USPT

Nov 30, 2004 

DOCUMENT-IDENTIFIER: US 6825185 B2

TITLE: Substituted aryl compounds as novel cyclooxygenase-2 selective inhibitors, compositions and methods of use

## CLAIMS:

7. The method of claim 6, wherein the disorder resulting from elevated levels of COX-2 is angiogenesis, arthritis, asthma, bronchitis, menstrual cramps, premature labor, tendonitis, bursitis, a skin-related condition, neoplasia, inflammation in disease, ophthalmic disorder, pulmonary inflammation, central nervous system disorder, allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis, inflammation, microbial infection, cardiovascular disorder, urinary disorder, urological disorder, endothelial dysfunction, a disorder treated by the preservation of organs and tissues, a disorder treated by inhibition of activation, adhesion and infiltration of neutrophils at the site of inflammation, or a disorder treated by inhibition of platelet aggregation.

17. The method of claim 16, wherein the compound of claim 2 or a pharmaceutically acceptable salt thereof, and the least one of a 3-hydroxy-3-methylglutaryl coenzyme A, an antiplatelet agent, a thrombin inhibitor or a thromboxane inhibitor are administered orally, buccally, topically, by injection, by inhalation, or by transdermal application.

28. The composition of claim 18, wherein the therapeutic agent is a steroid, a nonsteroidal antiinflammatory compound, a 5-lipoxygenase inhibitor, a leukotriene B.sub.4 receptor antagonist, a leukotriene A.sub.4 hydrolase inhibitor, a 5-HT agonist, a 3-hydroxy-3-methylglutaryl coenzyme A inhibitor, a H.sub.2 receptor antagonist, an antineoplastic agent, an antiplatelet agent, a thrombin inhibitor, a thromboxane inhibitor, a decongestant, a diuretic, a sedating or non-sedating anti-histamine, an inducible nitric oxide synthase inhibitor, an opioid, an analgesic, a Helicobacter pylori inhibitor, a proton pump inhibitor, an isoprostane inhibitor, or a mixture of two or more thereof.

30. The composition of claim 29, wherein the therapeutic agent is a steroid, a nonsteroidal antiinflammatory compound, a 5-lipoxygenase inhibitor, a leukotriene B.sub.4 receptor antagonist, a leukotriene A.sub.4 hydrolase inhibitor, a 5-HT agonist, a 3-hydroxy-3-methylglutaryl coenzyme A inhibitor, a H.sub.2 receptor antagonist, an antineoplastic agent, an antiplatelet agent, a thrombin inhibitor, a thromboxane inhibitor, a decongestant, a diuretic, a sedating or non-sedating anti-histamine, an inducible nitric oxide synthase inhibitor, an opioid, an analgesic, a Helicobacter pylori inhibitor, a proton pump inhibitor, an isoprostane inhibitor, or a mixture of two or more thereof.

33. The method of claim 32, wherein the disorder resulting from elevated levels of COX-2 is angiogenesis, arthritis, asthma, bronchitis, menstrual cramps, premature labor, tendonitis, bursitis, a skin-related condition, neoplasia, inflammation in disease, ophthalmic disorder, pulmonary inflammation, central nervous system disorder, allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis, inflammation, microbial infection, cardiovascular disorder, urinary disorder, urological disorder, endothelial dysfunction, a disorder treated by the preservation of organs and tissues, a disorder treated by inhibition of activation, adhesion and infiltration of neutrophils at the site of inflammation, or a disorder treated by inhibition of platelet aggregation.

42. The composition of claim 18, wherein the least one compound of claim 1 or a pharmaceutically acceptable salt thereof, the least one compound that donates, transfers or releases nitric oxide, or induces

the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase and the at least one therapeutic agents are administered orally, buccally, topically, by injection, by inhalation, or by transdermal application.

DERWENT-ACC-NO: 1995-106674  
DERWENT-WEEK: 199907  
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TITLE: Treating smooth or gastrointestinal muscle disorders - by direct injection of neurotoxin, pref. botulinum toxin A, for treating achalasia or menstrual cramps

Basic Abstract Text (1):

Treatment of smooth muscle disorders in a mammal comprises directly injecting an amt. of a neurotoxin (I) which inhibits neuro transmitter release from nerve terminals into a smooth muscle in the mammal.

Basic Abstract Text (2):

Also claimed is a device for injecting a drug into a target tissue in a target organ via an endoscope, including a hollow needle to pierce the target tissue, a deformable capsule to hold the drug, a piston to press the capsule so that drug is released through the needle and a retractable catheter sheath which encompasses the needle during insertion, where the needle is in direct contact with a first end of the capsule and the piston is in contact with a second end, both ends being within the sheath.

Basic Abstract Text (3):

USE - Conditions treated are: (a) gastrointestinal tract motility disorders, e.g. upper oesophageal sphincter disorder, achalasia, isolated disorders of the lower oesophageal disorder (LES), gastroparesis, hypertrophic pyloric stenosis, sphincter of Oddi dysfunction, levator syndrome, short-segment Hirschsprung's irritable bowel syndrome, and fissures, haemorrhoids or proctalgia fugax; or (b) other smooth muscle disorders. e.g. vasospastic or uterine or bladder spasm disorders such as menstrual and premenstrual cramps, a typical angina, Berger's disease or spastic bladder.

Equivalent Abstract Text (1):

In vivo treatment of smooth muscle disorders of a mammal comprises injecting a transmitter release inhibiting neurotoxin directly into a smooth muscle.

Equivalent Abstract Text (2):

Pref. the amt. of neurotoxin reduces spasm or tone of the muscle, and pref. inhibits acetylcholine release. Pref. the toxin is selected from botulinus toxin, tetanus toxin and tetrodotoxin.

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<input type="checkbox"/>	L10	l9 and (baloon or catheter or foley).ti,ab,clm.	8

END OF SEARCH HISTORY

DERWENT-ACC-NO: 2001-326811  
DERWENT-WEEK: 200410  
COPYRIGHT 2005 DERWENT INFORMATION LTD

TITLE: Methods for delivering medications to treatments sites provide controlled release of therapeutic agents through the use of a permeable hydrogel membrane as a reservoir for an inhalation fluid containing a therapeutic agent

Basic Abstract Text (7):

An INDEPENDENT CLAIM is also included for drug delivery catheters comprising:

Basic Abstract Text (13):

USE - The methods are used to treat aberrant cells and to treat cancer (claimed) including bladder, urethral, brain, mammarian and ovarian cancer, ischemia, benign prostatic hypertrophy and benign prostatic hyperplasia as well as symptoms caused by the release of toxins, gastritis, inflammation, coma, water retention, weight gain or loss, ischemia and immunodeficiency such as fever, nausea, diarrhea, weakness and headache.

Basic Abstract Text (14):

ADVANTAGE - The methods provide controlled release of therapeutic agents. The methods use membrane devices that can be used in conjunction with catheters or similar instruments with elongated hollow bodies such as venous and arterial conduits, endoscopes, cystoscopes, culpasopes, colonoscopes, trocars and laparoscopes.

Basic Abstract Text (16):

Drug delivery catheter 10

Basic Abstract Text (18):

catheter body 14

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DOCUMENT-IDENTIFIER: US 20030108597 A1

TITLE: Application of lipid vehicles and use for drug delivery

Abstract Paragraph:

The present invention relates to compositions and methods for the administration of lipid-based vehicles to treat various disorders, including bladder inflammation, infection, dysfunction, and cancer. In various aspects, the compositions and methods of the invention are useful for prolonged delivery of drugs, e.g., antibiotics, pain treatments, and anticancer agents, to the bladder, genitourinary tract, gastrointestinal system, pulmonary system, and other organs or body systems. In particular, the present invention relates to liposome-based delivery of vanilloid compounds, such as resiniferatoxin, capsaicin, or tinyatoxin, and toxins, such as botulinum toxin, for the treatment of bladder conditions, including pain, inflammation, incontinence, and voiding dysfunction. Further related are methods of using these vehicles alone or in conjunction with antibodies, e.g., uroplakin antibodies, to improve duration of liposome attachment, and provide a long-term intravesical drug delivery platform. The present invention specifically relates to antibody-coated liposomes that are useful for targeting specific receptors for drug, peptide, polypeptide, or nucleic acid delivery. In one particular aspect, the present invention relates to liposomes coated with antibodies against nerve growth factor (NGF) receptor and containing NGF antisense nucleic acids, which are used as a treatment for neurogenic bladder dysfunction.

Summary of Invention Paragraph:

[0002] The present invention relates to compositions and methods for the Instillation of lipid vehicles (e.g., micelles, microemulsions, macroemulsions, and liposomes) to treat various disorders, including bladder inflammation and dysfunction. The vehicles of the present invention are useful for prolonged delivery of drugs such as antibiotics and anticancer agents to the bladder, genitourinary tract, gastrointestinal system, pulmonary system, and other organs or body systems. Specifically, the present invention relates to liposome-based delivery of resiniferatoxin, capsaicin, tinyatoxin, and other vanilloid compounds for the treatment of bladder pain, inflammation, incontinence, and voiding dysfunction. Also related is liposome-based delivery of toxins, such as botulinum toxin, for the treatment of involuntary muscle contractions including those associated with urethral dyssynergia and bladder spasticity. The vehicles of the present invention are used alone or in conjunction with antibodies, e.g., uroplakin antibodies, that improve duration of liposome attachment, and provide a long-term intravesical delivery platform for drug, peptide, polypeptide, or nucleic acid delivery. In one aspect, the present invention relates to liposomes coated with antibodies against nerve growth factor (NGF) receptor and containing NGF antisense nucleic acids, which are useful as treatments for neurogenic bladder dysfunction.

Summary of Invention Paragraph:

[0018] The present invention encompasses improved treatments for pain (e.g., neuropathic pain), pain-intensive disorders (e.g., IC), muscle contraction disorders (e.g., IC, hyperactive bladder, and UDSD), and related conditions by providing compositions and methods for the intravesical administration of lipid vehicles. Liposomes provide non-toxic vehicles for the delivery of lipophilic therapeutic agents that have irritative side effects (e.g., vanilloids such as capsaicin) or undesirable antigenicity (e.g., botulinum toxin). Advantageously, the disclosed lipid vehicles can be used simultaneously deliver and ameliorate irritation caused by irritating therapeutic agents. The vehicles can also be used to reduce or prevent antibody-mediated resistance to antigenic therapeutic agents. In addition, the disclosed lipid vehicles can be utilized as an intravesical drug delivery platform for antibiotic and anticancer agents in the bladder and other luminal organ systems, e.g., the distal colon and vagina.

Summary of Invention Paragraph:

[0019] The invention includes compositions comprising lipid vehicles (e.g., micelles, microemulsions, macroemulsions, and liposomes) for use as intravesical instillation vehicles for cells or tissues. Such

therapeutic agents that have irritative side effects (e.g., vanilloids such as capsaicin) or undesirable antigenicity (e.g., botulinum toxin). Advantageously, the disclosed lipid vehicles can be used simultaneously deliver and ameliorate irritation caused by irritating therapeutic agents. The vehicles can also be used to reduce or prevent antibody-mediated resistance to antigenic therapeutic agents. In addition, the disclosed lipid vehicles can be utilized as an intravesical drug delivery platform for antibiotic and anticancer agents in the bladder and other luminal organ systems, e.g., the distal colon and vagina.

Summary of Invention Paragraph:

[0019] The invention includes compositions comprising lipid vehicles (e.g., micelles, microemulsions, macroemulsions, and liposomes) for use as intravesical instillation vehicles for cells or tissues. Such vehicles may further include antibodies, for example, uroplakin or NGF receptor antibodies. These antibodies may be conjugated to the surface of the liposome, and act to target the liposome to specific cell types and/or receptors. In addition, the vehicles may include compositions, including capsaicin, resiniferatoxin, tinyatoxin, and other vanilloids, which can be delivered to the cells. The vehicles may also include compositions comprising bioactive agents (e.g., antisense nucleic acids or peptides), drugs (e.g., pain therapeutics, anticancer treatments, or antibiotics), toxins (e.g., botulinum toxin), or other agents.

Summary of Invention Paragraph:

[0021] The invention also encompasses methods of treating pain (e.g., neuropathic pain) associated with cancers and/or disorders of the bladder, genitourinary tract, gastrointestinal tract, pulmonary system, and other body systems, using the disclosed lipid vehicles. In particular, the disclosed vehicles can be administered via intravesical instillation to treat pain associated with IC, or other conditions of the bladder, such as bladder infections and bladder cancer. In specific embodiments, these vehicles may comprise vanilloids, e.g., capsaicin, resiniferatoxin, or tinyatoxin, and may further comprise surface antibodies, e.g., uroplakin or NGF receptor antibodies, to target pain relief to the affected sites.

Detail Description Paragraph:

[0032] The present invention relates to the administration of lipid vehicles to provide long-lasting drug delivery to diseased or dysfunctional cells, tissues, or body systems. In particular, the invention relates to treatments for urinary system components, e.g., kidneys, ureters, bladders, sphincter muscles, and urethras. Specifically encompassed are treatments for bladder irritation and irritation-induced bladder dysfunction. In accordance with the present invention, nonionic liposomes are formulated to act as a drug with prolonged efficacy for topical bladder instillation, and bladder-protective effects. The efficacy and protective effects of such formulations are unexpected and surprising results. Advantageously, the disclosed liposome vehicles can be used to simultaneously deliver and ameliorate irritation caused by irritating therapeutic agents, e.g., resiniferatoxin or other vanilloid agents. The disclosed methods of intravesical administration of liposomes provide novel treatments for IC patients. Such methods can also be employed for the treatment of other disorders of the urinary system, bladder, genitourinary tract, gastrointestinal tract, pulmonary system, and other body organs and systems, including cancers, infections, and spasticity.

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File: PGPB

Jun 12, 2003

DOCUMENT-IDENTIFIER: US 20030108597 A1

TITLE: Application of lipid vehicles and use for drug delivery

Abstract Paragraph:

The present invention relates to compositions and methods for the administration of lipid-based vehicles to treat various disorders, including bladder inflammation, infection, dysfunction, and cancer. In various aspects, the compositions and methods of the invention are useful for prolonged delivery of drugs, e.g., antibiotics, pain treatments, and anticancer agents, to the bladder, genitourinary tract, gastrointestinal system, pulmonary system, and other organs or body systems. In particular, the present invention relates to liposome-based delivery of vanilloid compounds, such as resiniferatoxin, capsaicin, or tinyatoxin, and toxins, such as botulinum toxin, for the treatment of bladder conditions, including pain, inflammation, incontinence, and voiding dysfunction. Further related are methods of using these vehicles alone or in conjunction with antibodies, e.g., uroplakin antibodies, to improve duration of liposome attachment, and provide a long-term intravesical drug delivery platform. The present invention specifically relates to antibody-coated liposomes that are useful for targeting specific receptors for drug, peptide, polypeptide, or nucleic acid delivery. In one particular aspect, the present invention relates to liposomes coated with antibodies against nerve growth factor (NGF) receptor and containing NGF antisense nucleic acids, which are used as a treatment for neurogenic bladder dysfunction.

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Summary of Invention Paragraph:

[0018] The present invention encompasses improved treatments for pain (e.g., neuropathic pain), pain-intensive disorders (e.g., IC), muscle contraction disorders (e.g., IC, hyperactive bladder, and UDSD), and related conditions by providing compositions and methods for the intravesical administration of lipid vehicles. Liposomes provide non-toxic vehicles for the delivery of lipophilic

vehicles may further include antibodies, for example, uroplakin or NGF receptor antibodies. These antibodies may be conjugated to the surface of the liposome, and act to target the liposome to specific cell types and/or receptors. In addition, the vehicles may include compositions, including capsaicin, resiniferatoxin, tinyatoxin, and other vanilloids, which can be delivered to the cells. The vehicles may also include compositions comprising bioactive agents (e.g., antisense nucleic acids or peptides), drugs (e.g., pain therapeutics, anticancer treatments, or antibiotics), toxins (e.g., botulinum toxin), or other agents.

Summary of Invention Paragraph:

[0021] The invention also encompasses methods of treating pain (e.g., neuropathic pain) associated with cancers and/or disorders of the bladder, genitourinary tract, gastrointestinal tract, pulmonary system, and other body systems, using the disclosed lipid vehicles. In particular, the disclosed vehicles can be administered via intravesical instillation to treat pain associated with IC, or other conditions of the bladder, such as bladder infections and bladder cancer. In specific embodiments, these vehicles may comprise vanilloids, e.g., capsaicin, resiniferatoxin, or tinyatoxin, and may further comprise surface antibodies, e.g., uroplakin or NGF receptor antibodies, to target pain relief to the affected sites.

Detail Description Paragraph:

[0032] The present invention relates to the administration of lipid vehicles to provide long-lasting drug delivery to diseased or dysfunctional cells, tissues, or body systems. In particular, the invention relates to treatments for urinary system components, e.g., kidneys, ureters, bladders, sphincter muscles, and urethras. Specifically encompassed are treatments for bladder irritation and irritation-induced bladder dysfunction. In accordance with the present invention, nonionic liposomes are formulated to act as a drug with prolonged efficacy for topical bladder instillation, and bladder-protective effects. The efficacy and protective effects of such formulations are unexpected and surprising results. Advantageously, the disclosed liposome vehicles can be used to simultaneously deliver and ameliorate irritation caused by irritating therapeutic agents, e.g., resiniferatoxin or other vanilloid agents. The disclosed methods of intravesical administration of liposomes provide novel treatments for IC patients. Such methods can also be employed for the treatment of other disorders of the urinary system, bladder, genitourinary tract, gastrointestinal tract, pulmonary system, and other body organs and systems, including cancers, infections, and spasticity.

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L14: Entry 21 of 25

File: USPT

Dec 16, 1997

DOCUMENT-IDENTIFIER: US 5698549 A

TITLE: Method of treating hyperactive voiding with calcium channel blockers

Detailed Description Text (22):

Significant increase in nerve fibers in the sub-urothelial and detrusor muscle layers in patients with IC, but not those with lupus-associated cystitis, indicates neurotrophic involvement. Cell types associated with IC inflammation, including mast cells, release substances that promote neural growth. Cystolysis, however reversed the sub-urothelial nerve proliferation. Many treatments for IC are based upon bladder de-afferentation, high-lighting the importance of this pathway in symptoms. Intravesical infusions of the sensory neurotoxin capsaicin have also been reported to reverse irritative voiding in IC, suggesting removal of the capsaicin-sensitive afferents ameliorates the symptoms. However, these treatments may ultimately be self-defeating. In the rat, denervation of the hemi-bladder increases bladder NGF and causes the remaining neurons to grow. An increased nerve fiber density is precisely what results from an increased supply of potent neurotrophic factors. Because neurotrophic factors regulate neural growth and afferent signaling in the adult, a role for factor-mediated neural changes is likely, before and after treatment. Therefore, it appears that bladder afferents grow and alter their responsive signaling after acute and chronic inflammatory stimuli in animals, and that IC in humans is also accompanied by nerve growth. Reinnervation can explain why the IC symptoms return or worsen after many treatments that could potentially cause denervation.

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DOCUMENT-IDENTIFIER: US 6579870 B2

TITLE: Bis-arylsulfones

## CLAIMS:

28. The method of claim 18 or 20 wherein said disease or disorder is obesity, depression, schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, a stress related disease, panic disorder, a phobia, obsessive compulsive disorder, post-traumatic-stress syndrome, immune system depression, major depression, a stress induced problem with the urinary, gastrointestinal or cardiovascular system, neurodegenerative disorders, autism, chemotherapy-induced vomiting, hypertension, migraine headaches, cluster headaches, sexual dysfunction in a mammal, addictive disorder and withdrawal syndrome, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, attention-deficit hyperactivity disorder, behavioral disturbance, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, conduct disorder, cyclothymic disorder, dysthymic disorder, fibromyalgia and other somatoform disorders, generalized anxiety disorder, an inhalation disorder, an intoxication disorder, movement disorder, oppositional defiant disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, mood disorder, seasonal affective disorder, a sleep disorder, cognitive disorders, irritable bowel syndrome, a specific developmental disorder, agitation disorder, selective serotonin reuptake inhibition (SSRI) "poop out" syndrome or Tourette's syndrome.

29. The method of claim 18 or 20 wherein said compound is administered rectally, topically, nasally, sublingually, transdermally or parenterally.

4



DOCUMENT-IDENTIFIER: US 6123703 A

TITLE: Ablation catheter and methods for treating tissues

CLAIMS:

1. An ablation catheter system comprising:

a delivery catheter having a distal section, a distal end, a proximal end, and at least one lumen extending therebetween, wherein the delivery catheter has at least one opening at the distal section;

a handle attached to the proximal end of the delivery catheter, wherein the handle has a cavity;

an inner catheter located within the at least one lumen of the delivery catheter, the inner catheter having a tip section, a distal end and a proximal end;

a retractable metallic element means mounted on the tip section of the inner catheter, wherein the retractable metallic element means is preshaped and preformed in a close loop fashion and is wrapped around the distal section of the delivery catheter, and wherein an electrical conductor is connected to the retractable metallic element means;

an electrode deployment means mounted on the handle, wherein the electrode deployment means is attached to the proximal end of the inner catheter; and

a RF energy generating means, wherein the RF energy is provided through the electrical conductor to the retractable metallic element means.

3. The ablation catheter system of claim 1, wherein the at least one lumen of the delivery catheter has at least one opening at the distal end of the delivery catheter.

10. A rapid exchange balloon catheter system, comprising:

a delivery catheter having a plurality of lumens, wherein the plurality of lumens include an inflation lumen, the inflation lumen having a proximal end and a distal end, and wherein the delivery catheter has an opening at the distal section;

an inflatable balloon having a proximal end and a distal end;

a handle attached to the proximal end of the delivery catheter, wherein the handle has a cavity;

a wire guide shaft defining a wire guide lumen, the wire guide shaft having a proximal end and a distal end, wherein the proximal end of the wire guide shaft is distal to the distal end of the inflatable balloon;

an inner catheter located within one of the plurality of lumens of the delivery catheter, the inner catheter having a tip section, a distal end and a proximal end;

a retractable metallic element means mounted on the tip section of the inner catheter, the retractable metallic element means having a distal end and a proximal end, wherein the retractable metallic element means folds and wraps onto the tip section of the inner catheter, wherein the distal end of the retractable metallic element means is proximal to the proximal end of the inflatable balloon, and wherein an electrical conductor is connected to the retractable metallic element means;

an element deployment means mounted on the handle, wherein the element deployment means is attached to the proximal end of the inner catheter;

a catheter tip having proximal and distal ends, wherein the distal end of the inflation lumen opens into and is in communication with an interior of the inflatable balloon, the distal end of the inflatable balloon is sealed by the proximal end of the catheter tip, and the wire guide shaft is coupled only to the catheter tip completely distally of the distal end of the inflatable balloon; and

a RF current generator means, wherein the RF current is provided through the electrical conductor to the retractable metallic element means.

17. A method for inserting an ablation catheter system in a patient for treating the tissues, the ablation catheter system comprising a delivery catheter having a distal section, a distal end, a proximal end, and at least one lumen extending therebetween, wherein the delivery catheter has an opening at the distal section; a handle attached to the proximal end of the delivery catheter, wherein the handle has a cavity; an inner catheter located within the at least one lumen of the delivery catheter, the inner catheter having a tip section, a distal end and a proximal end; a retractable metallic element means mounted on the tip section of the inner catheter, wherein the retractable metallic element means is preshaped and preformed in a close loop fashion and is wrapped around the distal section of the delivery catheter, and wherein an electrical conductor is connected to the retractable metallic element means; an electrode deployment means mounted on the handle, wherein the electrode deployment means is attached to the proximal end of the inner catheter; and a RF energy generating means, wherein the RF energy is provided through the electrical conductor to the retractable metallic element means;

the method comprising the steps of:

- (a) inserting the ablation catheter through a natural opening to the location of the tissue for treatment;
- (b) deploying the retractable metallic element means of the inner catheter to circumferentially extend the retractable metallic element means, adapted to contact the tissues; and
- (c) applying RF energy to the retractable metallic element means to effect treatment of the tissues.

18. The method for treating tissues of a patient as in claim 17, the ablation catheter further comprising a fluid duct within the lumen of the inner catheter, the fluid duct having a proximal end and a distal end, the distal end of the fluid duct being connected to the retractable metallic element means, wherein the fluid is supplied to the retractable metallic element means, and wherein the retractable metallic element is made of a porous metal.

19. The method for treating tissues of a patient as in claim 18, wherein the fluid is selected from the group consisting of a serotonin antagonist, a cyclooxygenase inhibitor, an endothelin antagonist, an ATP-sensitive K<sub>sup.</sub>+ channel antagonist, a Ca<sub>sup.</sub>2+ channel antagonist, a nitric oxide donor, an anti-thrombin agent, a glycoprotein IIb/IIIa receptor blocker, a PKC inhibitor and a protein tyrosine kinase inhibitor.



US005861431A

# United States Patent [19]

## Hildebrand et al.

[11] Patent Number: **5,861,431**  
 [45] Date of Patent: **\*Jan. 19, 1999**

### [54] INCONTINENCE TREATMENT

[75] Inventors: Keith R. Hildebrand, Houlton, Wis.;  
 Jan Ellen O. Fowler, St. Paul; Dezzo  
 K. Levlus, Bloomington, both of Minn.

[73] Assignee: Iotek, Inc., Minneapolis, Minn.

[\*] Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

[21] Appl. No.: 477,474

[22] Filed: **Jun. 7, 1995**

[51] Int. Cl.<sup>6</sup> ..... A61K 31/19  
 [52] U.S. Cl. .... 514/557; 514/558; 514/559;  
 514/560; 514/561; 514/562; 514/563; 514/564;  
 514/565; 514/566; 514/567; 514/568; 514/569;  
 514/570; 514/571; 514/572; 514/573; 514/574  
 [58] Field of Search ..... 514/552, 558,  
 514/559, 560, 561, 562, 563, 564, 565,  
 566, 567, 568, 569, 570, 571, 572, 573,  
 574

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#### [57] ABSTRACT

The present invention provides a method of treating incontinence in a patient that has a bladder and a urethra. The urethra forms a lumen for draining the bladder. The method comprises the steps of delivering an agent into the lumen and passing the agent from the lumen to internal body tissue. The agent increases restriction of the lumen thereby providing increased control over urine flow from the bladder.

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FIG. 1

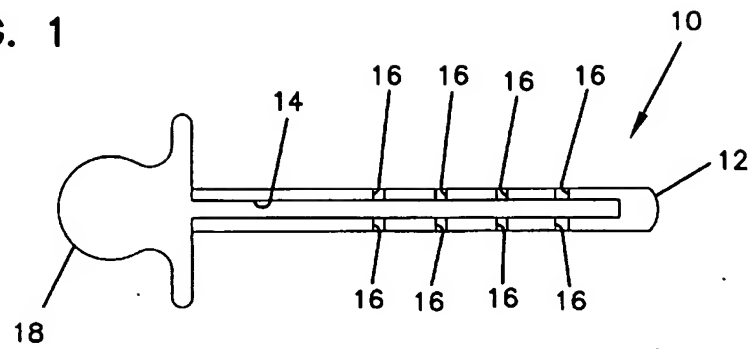


FIG. 2

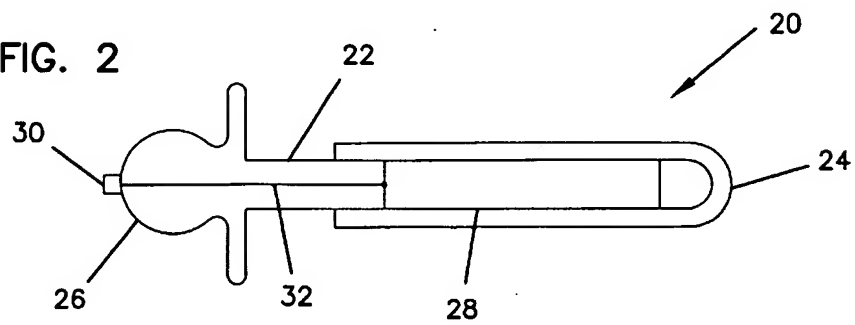


FIG. 3

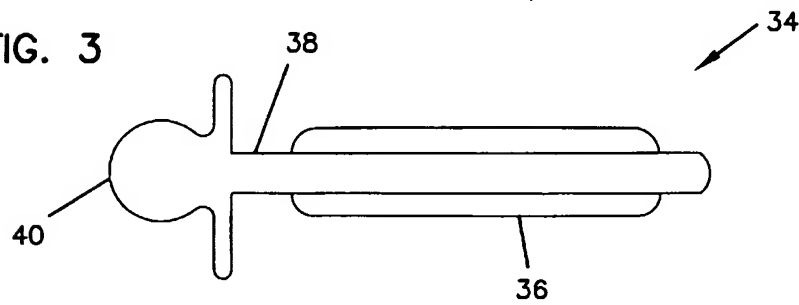


FIG. 4

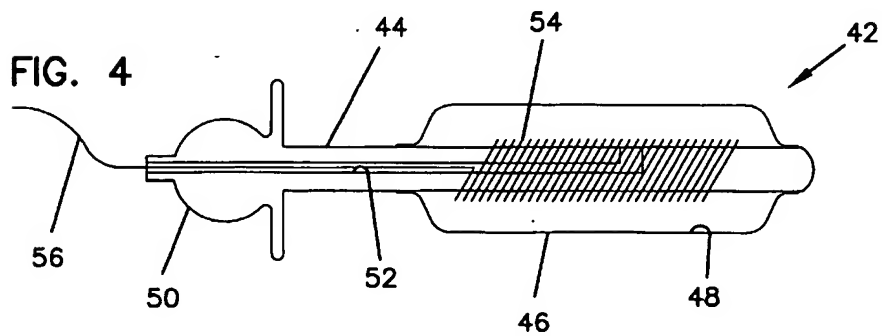
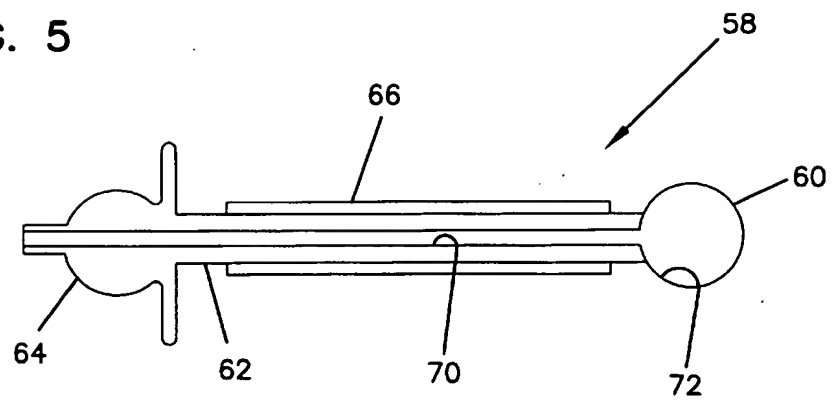


FIG. 5



## INCONTINENCE TREATMENT

## TECHNICAL FIELD

The present invention relates to the delivery of an agent, and more particularly to intraurethral delivery of an agent for treating incontinence.

## BACKGROUND

Urinary incontinence is an involuntary discharge of urine from the bladder. Incontinence can be caused by a variety of factors including pregnancy, estrogen deficiency, general weakening of the sphincter or pelvic floor muscles, surgery along the urinary tract, infection, and other maladies localized in the urinary tract. This condition is widespread and affects millions of people.

There are several types of incontinence including stress incontinence, urge incontinence, and total incontinence. Stress incontinence occurs when a person's body is under physical stress. People suffering from this type of incontinence might experience urine discharge during physically stressful events. Examples of stressful events include coughing, laughing, and rigorous exercise. Urge incontinence is characterized as an urgent desire to urinate and results in total discharge of the bladder. This type of incontinence can occur at any time, but frequently occurs when a person has a sudden change in their physical position. Total incontinence is characterized by a total lack of control over urine discharge and is frequently caused by a complete failure of the sphincter muscles.

Current treatments for incontinence vary widely. Many people have to wear protective underwear such as diapers or a urinary catheter that collects discharged urine. These types of control can be uncomfortable, unsightly, and socially awkward. Pelvic exercises are also used to strengthen weak pelvic muscles. However, such exercises have limited affect, especially if the person does not perform the exercises properly or on a regular basis. Additionally, surgery is often performed to tighten the sphincter muscles. Surgery is a rather severe treatment and is typically performed as a last resort if all other treatments fail.

Drug therapy is another alternative treatment for incontinence. The type of drug that is used can vary depending on the type and cause of incontinence. For example, menopausal and post-menopausal women often experience estrogen deficiency, which causes a variety of symptoms including a thinning of the urethral and vaginal mucosa. Thinning of the urethral mucosa can result in a lack of urethral pressure and thus stress incontinence. Estrogen replacement therapy may help to control menopause related incontinence because some of the estrogen will reach and stimulate the estrogen receptors in the urethral wall. The stimulation will trigger an increase in the thickness of the urethral mucosa, which increases urethral pressure and helps to control incontinence.

In practice, estrogen is administered vaginally, orally, or transdermally. These forms of administration can cause serious side effects because the estrogen is exposed to normal and healthy tissue outside the urinary tract, which is the desired treatment area. Examples of possible side effects include breast tenderness, vaginal bleeding, cancer such as endometrial carcinoma, susceptibility to hypertension, and risk of abnormal blood clotting. The risk of side effects is even greater if there is sustained use of estrogen over a prolonged period. Therefore, estrogen replacement therapy may carry too much risk if the only or main goal of the therapy is to treat incontinence.

Another problem with estrogen replacement therapy is that tissue other than the urethral wall will absorb a significant portion of the dose. Thus, a larger dose must be administered in order to get an effective amount of estrogen to the urinary tract. The difficulty is that use of a larger dose of estrogen increases the risk of side effects and also causes an increase in the amount of waste because tissue outside the target area will absorb a larger amount of estrogen.

Other agents that increase the tone of the internal and external sphincter muscles may be used to treat incontinence. Examples of these agents include sympathomimetics such as  $\alpha$ -adrenergic agonists and nicotinic cholinergic agonists. However, current methods of delivering these agents have problems similar to the method for delivering estrogens. That is, areas outside the urinary tract are exposed to the agent, which increases the risk of side effects. For example, sympathomimetics can result in elevated blood pressure, stimulation of the central nervous system resulting in insomnia and anxiety, dizziness, tremors, and cardiac arrhythmias. Nicotinic cholinergic agonists can also have harmful effects because there are nicotinic cholinergic receptors in the skeletal muscles, autonomic ganglia, and the adrenal medulla. Thus, treatment using nicotinic cholinergic agonists also can cause a variety of side effects.

Incontinence and current methods for treating incontinence can have a very harmful effect on a person's social, psychological, and physical well being. The involuntary discharge of urine in a public place is embarrassing if the person is not wearing any type of protective underwear or a collection catheter. It can also cause great discomfort. As a result, many people might limit their social interaction outside the privacy of their home. Even if people do wear protective underwear or a catheter, they often cause unsightly and telling bulges in the clothing. Other forms of control also have limitations. For example, many people do not perform pelvic exercises properly or on a regular basis, which limits the exercise's effectiveness. Additionally, surgery can be dangerous and is only performed as a last result.

Regarding the use of agents for treating incontinence, current delivery techniques expose the agent to tissue outside of the desired treatment area, which is an inefficient use of the agent and dramatically increases the risk of side effects. Therefore, there is a need in the art for a method of delivering an agent that can treat incontinence with a reduced risk of side effects.

## SUMMARY

The present invention is a method for treating incontinence in a patient that has a bladder and a urethra. The urethra forms a lumen for draining the bladder. The method includes the steps of delivering an agent into the lumen and passing the agent from the lumen to internal body tissue. The agent increases restriction of the lumen, thereby providing increased control over urine flow from the bladder.

## DETAILED DESCRIPTION OF THE DRAWINGS

Illustrated embodiments of the devices used to perform the present invention will be described in detail with reference to the drawings, where like reference numerals represent the like parts and assemblies throughout several views.

FIG. 1 shows a delivery device useful with the present invention, the delivery device having a suction bulb for storing and discharging an agent;

FIG. 2 shows a delivery device useful with the present invention, the delivery device having an absorbent sheath for retaining an agent and iontophoretic electrode;

FIG. 3 shows a suppository and a tool useful with the present invention, the tool for inserting the suppository into the urethra;

FIG. 4 shows a delivery device useful with the present invention, the delivery device having a porous balloon and a lumen for inflating the balloon with an agent; and

FIG. 5 shows a plug type delivery device useful with the present invention, the delivery device having a balloon for blocking the neck of the bladder and an absorbent sheath for retaining an agent.

#### DETAILED DESCRIPTION

The invention initially will be described in general terms. The preferred embodiment of the invention will then be described in detail with reference to the drawings. Reference to the preferred embodiment does not limit the scope of the invention, which is limited only by the scope of the claims.

The present invention relates generally to direct intraurethral delivery of therapeutic agents that are effective for treating incontinence. Delivering a therapeutic agent directly through the urethra has several significant advantages. One advantage is that the agent is delivered directly to the receptors in the wall of the urethra and to the sphincter muscles. As a result, exposure of the agent to the reproductive organs as well as other parts of the body is diminished, which reduces the risk of side effects.

Minimizing the amount of agent that is delivered outside of the urinary tract also reduces waste. Thus, a smaller dose of the agent can be used with the present invention while increasing its effectiveness. In other words, the agent that is delivered into the patent will be used much more efficiently.

According to the present invention, the agent is delivered directly into the urethral lumen. The agent is then passed from the lumen into the wall of the urethra where it will cause an increase in urethral pressure. The agent accomplishes increased urethral pressure by one or more of the following: stimulating the estrogen receptors,  $\alpha$ -adrenergic receptors, nicotinic cholinergic receptors, or other urethral mechanism.

The agent can be contained in many different forms. For example, the agent can be delivered as a liquid, cream, solution, emollient, gel, or spray. Additionally, the therapeutic agent can be delivered in microparticles composed of various biocompatible, biodegradable polymers. Examples of these types of polymers include polyester, polyalkylcyanoacrylate, polyorthoester, polyanhydride, albumin, gelatin, and starch. An advantages of microparticles is that they provide controlled and sustained release of the agent thereby minimizing the required dosing frequency.

The type of agent that can be delivered depends on the desired results. For example, estrogens may increase urethral pressure by increasing the thickness of the urethral mucosa. Moreover, estrogens may increase the number of adrenergic receptors on urethral smooth muscle. The estrogen can have several different forms including natural, synthetic, or semi-synthetic compounds. Examples of estrogens include estradiol, diethyl stilbestrol, estrone, estrone sodium sulfate, sodium equilin sulfate, ethinyl estradiol, quinestril, diethylstilbestrol, mestranol, estriol, and chlorotrianisene. Although certain estrogens are set forth as an example, one skilled in the art will appreciate that other molecules will stimulate estrogen receptors and cause an increase in the thickness of the urethral mucosa.

Sympathomimetic agents generate urethral pressure by increasing the tone of the internal sphincter. The sympatho-

mimetic agent will stimulate the  $\alpha$ -adrenergic receptors in the internal sphincter, which will increase its tone. The internal sphincter will then tighten around the urethra and the neck of the bladder.

$\alpha$ -Adrenergic agonists are one type of sympathomimetic agent that can be effective. Various types of  $\alpha$ -adrenergic agents include phenylephrine HCl, pseudoephedrine HCl, phenylpropanolamine HCl, ephedrine sulfate, norephedrine HCl, xylometazoline HCl, oxymetazoline HCl, naphazoline HCl, norepinephrine HCl, and privityne HCl. Examples of other sympathomimetic agents include norepinephrine uptake inhibitors such as desipramine HCl, amitriptyline HCl, desmethylinipramine HCl, and imipramine HCl. Yet another sympathomimetic agent includes norepinephrine releasing agents such as tyramine. Although certain sympathomimetic agents are set forth as examples, one skilled in the art will appreciate that other agents will increase muscle tone of the internal sphincter and cause it to tighten around the urethra and the neck of the bladder. Although certain salts are specifically listed, one skilled in the art will further appreciate that other salts of the active ingredients can also be used.

Nicotinic cholinergic agonists and acetylcholinesterase inhibitors increase the tone of the external sphincter. Additionally, either of these types of agents can be combined with muscarinic cholinergic antagonist such as atropine, scopolamine, or glycopyrrolate. In this type of treatment, the agent will stimulate the nicotinic cholinergic receptors in the external sphincter, which will increase its tone and cause it to tighten around the urethra. Examples of nicotinic cholinergic agonists include choline, acetylcholine, methacholine, carbachol, bethanechol, arecoline, and \*1,1-dimethyl-4-phenylpiperazinium iodide. Examples of acetylcholinesterase inhibitors include physostigmine salicylate, neostigmine Br, ambenonium Cl, edrophonium Cl, demecarium Br, and pyridostigmine Br. Although certain nicotinic cholinergic agonists, acetylcholinesterases, and muscarinic cholinergic antagonists are set forth as examples, one skilled in the art will appreciate that other agents will cause the external sphincter muscle to increase its tone and tighten around the urethra. Although certain salts are listed, one skilled in the art will further appreciate that other salts of the active ingredients can also be used.

Additionally, estrogens and sympathomimetics such as an  $\alpha$ -adrenergic agonist can be used in combination. Current medical research indicates that estrogens may increase the number of  $\alpha$ -adrenergic receptors in the internal sphincter. Thus, the  $\alpha$ -adrenergic agonists will stimulate both the preexisting and newly developed  $\alpha$ -adrenergic receptors. The increased number of  $\alpha$ -adrenergic receptors will cause the sphincter muscles to respond more efficiently to the  $\alpha$ -adrenergic agonists and have an even greater increase in tone.

It may also be possible to treat urinary incontinence by delivering an agent such as a therapeutic gene. A therapeutic gene can be contained in a plasmid DNA together with a promoter. Genes could be delivered directly into the urethral wall using any of the embodiments or delivery techniques described in this specification. Because plasmids are large, highly negatively charged, and need to gain access to the intracellular compartment to be effective, devices that use iontophoresis to actively deliver the agent are preferred. Genes that encode for estrogen receptors, adrenergic receptors, or products that stimulate the growth of urethral mucosa, smooth muscle, or extracellular matrix could all potentially be used to increase the thickness of the mucosal lining of the urethra, the tone of the internal sphincter muscle, or the tone of the external sphincter muscle.



Other agents can be used that will enhance penetration of the therapeutic agent through the urothelium lining of the urethra and into the tissue of the urethral wall. The penetration enhancer may be mixed with the primary therapeutic agent for delivery. Examples of penetration enhancers include

dodecyl 2-(N,N-dimethylamino)propionate; 1,8-CN; 1-[2-(decylthio)ethyl]azacyclopentan-2-one; 1-dodecylazacycloheptan-2-one; oleic acid; dimethylsulfoxide; 1-menthol; and 1-lauryl-2-pyrrolidone. Two of those penetration enhancers, dodecyl 2-(N,N-dimethylamino)propionate and oleic acid, are ionic agents that are deliverable during iontophoresis. Although specific examples are provided, one skilled in the art will realize that there are other penetration enhancers that may be useful with the present invention.

Referring now to FIGS. 1-5, many different devices can be used with the present invention. The basic method can employ any of the devices shown in these figures in order to directly deliver the therapeutic agent into the urethral lumen and into the urethral wall. These devices can include either passive or active delivery mechanisms. Passive delivery mechanisms rely on principles such as diffusion and absorption. Examples of active delivery mechanisms include pressure, iontophoresis, electroporation, and phonophoresis.

Referring to FIG. 1, one possible delivery device 10 includes a hollow probe 12 that defines a chamber 14 and a plurality of perforations 16 that extend from the chamber 14 to the surface of the probe 12. The chamber 14 opens to the interior of the suction bulb 18. The suction bulb 18 is sized to prevent the probe 12 from being inserted too far into the urethra. In use, the person will dip the probe 12 into a reservoir of the therapeutic agent and draw a supply into the suction bulb 18. The probe 12 is then inserted into the urethra and the bulb 18 is compressed. Compressing the bulb 18 causes the therapeutic agent to discharge into the urethral lumen where it is absorbed into the urethral wall.

Referring to FIG. 2, another possible delivery device 20 provides iontophoretic delivery of the therapeutic agent. This device 20 includes a probe 22 that is covered by a sheath 24 formed from a polymer matrix, an open-cell foam, or a hydrogel. An applicator handle 26 is mounted on the end of the probe 22 to provide easy handling and to prevent the probe 22 from being inserted too far into the urethra. An electrode 28 is mounted on the surface of the probe 22 and beneath the sheath 24. A connector 30 is mounted on the handle 26 and a lead 32 extends between the connector 30 and the electrode 28. Iontophoretic delivery of an agent is well known in the art.

In use, the sheath 24 is loaded with the therapeutic agent and the probe 22 is then inserted into the urethral lumen. The agent can be loaded by dipping the probe 22 into a reservoir of the agent. The patient can load the sheath themselves. If greater control of the dose is required, however, the patient can purchase sheaths from a pharmacist that has preloaded the agent.

After the probe 22 is inserted into the urethral lumen, the agent is passed into the urethral wall. This task is accomplished by placing a second electrode (not shown) on the patient's skin and passing an electric current between the electrode 28 and the second electrode. The electric current will either drive or drag the agent into the urethral wall.

Although the electrode 22 is described for use with iontophoresis, it could also be used for electroporation, which is well known in the art. Another embodiment might replace the electrode with an ultrasonic transducer (not shown) for phonophoretic delivery of the agent, which is also well known in the art.

If active delivery is not desired, the probe does not need to include the electrode 28. In this alternative embodiment, the sheath 24 could be mounted on a removable urethral insert (not shown) that is deposited in the urethra for sustained release of the therapeutic agent. The probe 22 would act as an insertion tool for the urethral insert. Alternatively, the probe 22 can be left inserted in the urethra until the agent is passively delivered from the sheath into the urethral wall.

Referring to FIG. 3, a device 34 for passive delivery includes a suppository 36 and an insertion tool 38. The insertion tool 38 has a handle 40 that provides easy handling and is sized to prevent the insertion tool 38 from being inserted too far into the urethra. The tool 38 is used to insert the suppository 36 into the urethral lumen. The suppository 36 will contain the agent, which will be absorbed in the urethral wall.

Referring to FIG. 4, a delivery device 42 may include a probe 44 on which a porous balloon 46 is mounted. The balloon 46 defines a chamber 48. A handle 50 is attached to the probe 44 and is sized to prevent the probe 44 from being inserted too far into the urethra. The probe 44 defines a lumen 52 that extends from the handle 50 to the chamber 48 of the balloon 46. An electrode 54 is mounted on the probe 44 at a position within the chamber 48 of the balloon 46. A lead 56 is connected to the electrode 54 and extends through the lumen 52 for connection to a power supply (not shown). The electrode 54 could be replaced with an ultrasonic transducer (not shown) for phonophoretic delivery of the agent.

In use, the probe 44 is inserted into the urethral lumen. An agent is then injected into the chamber 48 via the lumen 52, which causes the balloon 46 to inflate and press against the urethral wall. Electric current is then caused to pass from the electrode 54 to another electrode (not shown) that is placed against the patient's skin. The current drives or drags the agent through the pores in the balloon 46 and into the urethral wall. Electroporation can also be used to enhance cellular uptake and penetration of the agent. The delivery device 42 can also be used without the electrode 54. In this alternative embodiment, the agent within the chamber is pressurized so that it will pass through the pores of the balloon 46 and be passively absorbed into the urethral wall.

Referring to FIG. 5, a delivery device 58 can include a balloon 60 for sealing the passage between the urethra and the bladder. This device is similar to the device shown in FIG. 2 and includes a probe 62, a handle 64 and a sheath 66, which is made from material such as a polymer matrix, an open-cell foam, or a hydrogel. The balloon 60 defines a chamber 72 and is mounted on the end of the probe 62 that is oppositely disposed from the handle 64. The balloon 60 is sized so that it fits through the neck of the bladder when deflated and blocks the passage between the bladder and urethra when inflated.

The probe 62 defines a lumen 70 that extends from the handle 64 to the chamber 72. An electrode (not shown) or an ultrasonic transducer (now shown) may be mounted on the probe 62.

The delivery device of FIG. 5 and associated delivery methods has several advantages. One advantage the device shown in FIG. 5 is that the balloon 60 can help to prevent the discharge of urine from the bladder before the effect of the therapeutic agent is realized. The therapeutic agents could cause the sphincter muscles to tighten around the probe 62 and reduce leakage even further. Thus, the delivery device could be left in the urethra for a period of time during sustained release of the therapeutic agent. If the probe 62 is

left in the urethra for an extended period, the handle 64 can be much smaller and/or flatter for increased comfort and in order to prevent unsightly bulges.

Another advantage of the delivery device 58 is that the balloon 60 prevents the therapeutic agent from being delivered into the bladder and affecting the detrusor smooth muscle surrounding the bladder. Preventing this type of delivery is important because the detrusor smooth muscle contains muscarinic cholinergic receptors, which may be stimulated by some of the agents that may be used to increase the tone of the external sphincter muscle. Thus, these agents may cause contraction of the detrusor smooth muscle, thereby compressing the bladder and causing involuntary discharge of urine. Acetylcholine is an example of an agent that will stimulate the muscarinic cholinergic receptors.

If there is a risk that the agent might stimulate the muscarinic cholinergic receptors, an alternative to using the device shown in FIG. 5 is to use a precise form of delivery that will minimize the bladder's exposure to the agent. This type of delivery might utilize a cream, suppository, or iontophoresis. Another alternative is to mix the agent with a muscarinic antagonist, which will block the muscarinic cholinergic receptors to prevent stimulation by the agent. The muscarinic antagonist will not block the nicotinic cholinergic receptors and thus not prevent the agent from increasing the tone of the external sphincter muscle.

The devices described above are presented for purposes of example only and are not intended to limit the scope of the present invention. One skilled in the art will understand that there may be other devices capable of delivering the agent in and to the urethra and then passing the agent into the urethral wall.

It is anticipated that the agents, devices, and delivery method described above can be administered by the patient as needed. Some of the agents may provide significant improvements for long periods of time with a single application possibly up to 8-12 hours. Other agents may require delivery several times over the course of the day. Additionally, some agents might require application for an extended period before urethral pressure begins to significantly increase. Estrogen is an example of an agent that will require extended application before thickness of the urethral mucosa is developed and a significant benefit is realized.

Although the description of the preferred embodiments and methods have been quite specific, it is contemplated that various modifications could be made without deviating from the spirit of the present invention. Accordingly, it is intended that the scope of the present invention be dictated by the appended claims, rather than by the description of the preferred embodiments and methods.

The invention that we claim is:

1. A method of treating incontinence in a patient, the patient having a bladder and a urethra, the urethra forming a lumen for draining the bladder, the method comprising the steps of:

delivering an agent into the lumen, the agent being selected from the group consisting of estrogenic hormones, sympathomimetics, acetylcholinesterases, and cholinergic agonists; and

passing the agent from the lumen to internal body tissue, the agent increasing restriction of the lumen thereby providing increased control over urine flow from the bladder.

2. The method of claim 1 wherein the internal body tissue includes estrogen receptors, further wherein the step of passing the agent from the lumen to internal body tissue

comprises the step of stimulating the estrogen receptors thereby increasing thickness of a urethral mucosa.

3. The method of claim 1 wherein the step of delivering an agent comprises the step of delivering an estrogenic hormone.

4. The method of claim 3 wherein the step of delivering an estrogenic hormone comprises the step of delivering an estrogenic hormone selected from the group consisting of: estradiol, diethyl stilbesterol, estrone, sodium estrone sulfate, sodium equilin sulfate, ethinyl estradiol, quinestrol, diethylstilbesterol, mestranol, estriol, and chlorotrianisene.

5. The method of claim 1 wherein the step of delivering an agent comprises the step of delivering a sympathomimetic.

6. The method of claim 5 wherein the step of delivering a sympathomimetic comprises the step of delivering a norepinephrine uptake inhibitor selected from the group consisting of: desipramine, amitriptyline, desmethylinipramine, and imipramine.

7. The method of claim 5 wherein the step of delivering a sympathomimetic comprises the step of delivering a norepinephrine releasing agent.

8. The method of claim 1 wherein the internal body tissue comprises an external sphincter muscle and nicotinic cholinergic receptors, further wherein the step of passing the agent from the lumen to internal body tissue comprises the step of stimulating the nicotinic cholinergic receptors thereby increasing the tone of the external sphincter muscle.

9. The method of claim 8 wherein the step of delivering an agent comprises the step of delivering an acetylcholinesterase inhibitor.

10. The method of claim 9 wherein the step of delivering an acetylcholinesterase inhibitor comprises the step of delivering an acetylcholinesterase inhibitor selected from the group consisting of: physostigmine, neostigmine, ambenonium, edrophonium, demecarium, and pyridostigmine.

11. The method of claim 1 wherein the step of delivering an agent comprises the step of delivering a nicotinic cholinergic agonist.

12. The method of claim 11 wherein the step of delivering a nicotinic cholinergic agonist comprises the step of delivering a nicotinic cholinergic agonist selected from the group consisting of: choline, acetylcholine, methacholine, carbachol, bethanechol, arecoline, and \*1,1-dimethyl-4-phenylpiperazinium iodide.

13. The method of claim 1 wherein the step of delivering an agent comprises delivering a cholinergic agonist, the method comprising the additional steps of:

delivering a muscarinic cholinergic antagonist into the lumen; and

passing the muscarinic cholinergic antagonist from the lumen to internal body tissue.

14. The method of claim 1 comprising the additional steps of:

delivering a penetration enhancing agent into the lumen; and

passing the penetration enhancing agent from the lumen to internal body tissue.

15. The method of claim 14 wherein the steps of delivering an agent and delivering a penetration enhancer into the lumen are performed simultaneously and the steps of passing the agent and passing the penetration enhancer are performed simultaneously.

16. The method of claim 15 wherein the step of delivering the penetration enhancer into the lumen comprises the step of selecting the penetration enhancer from the group con-

*Agents*

sisting of: dodecyl 2-(N,N-dimethylamino)propionate, 1,8-CN; 1-azacyclopentan-2-one; 1-dodecylazacycloheptan-2-one; oleic acid; dimethylsulfoxide; 1-menthol; and 1-lauryl-2-pyrrolidone.

17. The method of claim 1 comprising the additional step of substantially sealing the opening from the lumen into the bladder before the step of delivering the agent into the lumen.

18. The method of claim 1 wherein the agent is in a fluid state and the step of passing the agent from the lumen to the internal body tissue comprises the steps of:

placing a first electrode in the lumen;  
placing a second electrode in contact with the patient's body; and

transmitting an electrical current between the first and second electrodes such that the electrical current passes from the lumen into the internal body tissue.

19. The method of claim 1 wherein the agent is in a fluid state and the step of passing the agent from the lumen to the internal body tissue comprises the steps of pressurizing the fluid within the lumen.

20. The method of claim 1 wherein the agent is in a fluid state and the step of passing the agent from the lumen to the internal body tissue comprises the steps of:

placing an ultrasonic transducer in the lumen; and  
emitting ultrasonic waves from the transducer such that the ultrasonic waves propagate into the internal body tissue.

21. The method of claim 1 wherein the agent is in a suppository and the step of delivering the agent into the lumen comprises the step of placing the suppository in the lumen.

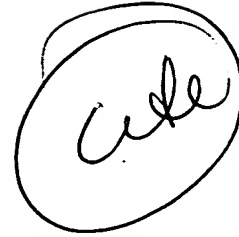
22. The method of claim 1 wherein the urethra has a wall that defines the lumen and the agent is in a cream, further wherein the step of delivering the agent into the lumen comprises the step of applying the cream to the wall of the urethra.

23. The method of claim 1 wherein the step of delivering an agent into the lumen comprises spraying the agent into the lumen.

\* \* \* \* \*

DOCUMENT-IDENTIFIER: US 5861431 A

Treatment: Incontinence treatment



## CLAIMS:

1. A method of treating incontinence in a patient, the patient having a bladder and a urethra, the urethra forming a lumen for draining the bladder, the method comprising the steps of:

delivering an agent into the lumen, the agent being selected from the group consisting of estrogenic hormones, sympathomimetics, acetylcholinesterases, and cholinergic agonists; and

passing the agent from the lumen to internal body tissue, the agent increasing restriction of the lumen thereby providing increased control over urine flow from the bladder.

2. The method of claim 1 wherein the internal body tissue includes estrogen receptors, further wherein the step of passing the agent from the lumen to internal body tissue comprises the step of stimulating the estrogen receptors thereby increasing thickness of a urethral mucosa.

6. The method of claim 5 wherein the step of delivering a sympathomimetic comprises the step of delivering a norepinephrine uptake inhibitor selected from the group consisting of: desipramine, amitriptyline, desmethylinipramine, and imipramine.

8. The method of claim 1 wherein the internal body tissue comprises an external sphincter muscle and nicotinic cholinergic receptors, further wherein the step of passing the agent from the lumen to internal body tissue comprises the step of stimulating the nicotinic cholinergic receptors thereby increasing the tone of the external sphincter muscle.

13. The method of claim 1 wherein the step of delivering an agent comprises delivering a cholinergic agonist, the method comprising the additional steps of:

delivering a muscarinic cholinergic antagonist into the lumen; and

passing the muscarinic cholinergic antagonist from the lumen to internal body tissue.

14. The method of claim 1 comprising the additional steps of:

delivering a penetration enhancing agent into the lumen; and

passing the penetration enhancing agent from the lumen to internal body tissue.

15. The method of claim 14 wherein the steps of delivering an agent and delivering a penetration enhancer into the lumen are performed simultaneously and the steps of passing the agent and passing the penetration enhancer are performed simultaneously.

16. The method of claim 15 wherein the step of delivering the penetration enhancer into the lumen comprises the step of selecting the penetration enhancer from the group consisting of: dodecyl 2-(N,N-dimethylamino)propionate, 1,8-CN; 1-azacyclopentan-2-one; 1-dodecylazacycloheptan-2-one; oleic acid; dimethylsulfoxide; 1-menthol; and 1-lauryl-2-pyrrolidone.

17. The method of claim 1 comprising the additional step of substantially sealing the opening from the

into the bladder before the step of delivering the agent into the lumen.

18. The method of claim 1 wherein the agent is in a fluid state and the step of passing the agent from the lumen to the internal body tissue comprises the steps of:

placing a first electrode in the lumen;

placing a second electrode in contact with the patient's body; and

transmitting an electrical current between the first and second electrodes such that the electrical current passes from the lumen into the internal body tissue.

19. The method of claim 1 wherein the agent is in a fluid state and the step of passing the agent from the lumen to the internal body tissue comprises the steps of pressurizing the fluid within the lumen.

20. The method of claim 1 wherein the agent is in a fluid state and the step of passing the agent from the lumen to the internal body tissue comprises the steps of:

placing an ultrasonic transducer in the lumen; and

emitting ultrasonic waves from the transducer such that the ultrasonic waves propagate into the internal body tissue.

21. The method of claim 1 wherein the agent is in a suppository and the step of delivering the agent into the lumen comprises the step of placing the suppository in the lumen.

22. The method of claim 1 wherein the urethra has a wall that defines the lumen and the agent is in a cream, further wherein the step of delivering the agent into the lumen comprises the step of applying the cream to the wall of the urethra.

23. The method of claim 1 wherein the step of delivering an agent into the lumen comprises spraying the agent into the lumen.



US006464697B1

(12) **United States Patent**  
**Edwards et al.**

(10) Patent No.: **US 6,464,697 B1**  
 (45) Date of Patent: **\*Oct. 15, 2002**

(54) **STOMACH AND ADJOINING TISSUE  
 REGIONS IN THE ESOPHAGUS**

(75) Inventors: **Stuart Edwards, Portala Valley; John  
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 San Carlos; Scott West, Livermore; Jay  
 Chln, Fremont, all of CA (US)**

(73) Assignee: **Curon Medical, Inc., Sunnyvale, CA  
 (US)**

(\*) Notice: Subject to any disclaimer, the term of this  
 patent is extended or adjusted under 35  
 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal dis-  
 claimer.

(21) Appl. No.: **09/304,737**

(22) Filed: **May 4, 1999**

**Related U.S. Application Data**

(63) Continuation-in-part of application No. 09/026,296, filed on  
 Feb. 19, 1998, now Pat. No. 6,009,877.

(51) Int. Cl.<sup>7</sup> ..... **A61B 18/18**

(52) U.S. Cl. .... **606/41; 607/101**

(58) Field of Search ..... **606/41, 42, 45-50;  
 607/101, 102, 115, 116, 133, 122**

(56) **References Cited**

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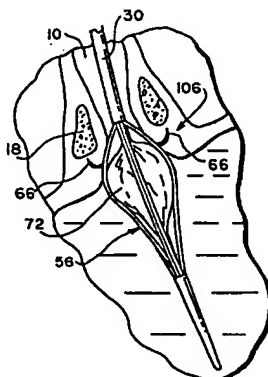
Primary Examiner—Michael Peffley

(74) Attorney, Agent, or Firm—Ryan Kromholz & Manion,  
 S.C.

(57) **ABSTRACT**

Systems and methods treat a tissue region. In one  
 arrangement, the systems and methods deploy an electrode  
 on a support structure in a tissue region at or near the cardia  
 of the stomach. The support structure has a proximal region  
 and a distal region. The proximal region is enlarged in  
 comparison to the distal region, and the electrode is carried  
 by the enlarged proximal surface. The systems and methods  
 advance the electrode in a path to penetrate the tissue region  
 and couple the electrode to a source of radio frequency  
 energy to ohmically heat tissue and create a lesion in the  
 tissue region. In another arrangement, the systems and  
 methods treat abnormal epithelium tissue at or near the  
 lower esophageal sphincter by bringing an array of surface  
 electrodes into contact with abnormal epithelium tissue. The  
 systems and methods couple the surface electrodes to a  
 source of radio frequency energy to ohmically heat tissue  
 and cause necrosis of the abnormal epithelium tissue.

**7 Claims, 41 Drawing Sheets**



0013264340 BIOSIS NO.: 200100436179

Botulinum-A toxin in the treatment of detrusor hyperreflexia

AUTHOR: Del Popolo Giulio (Reprint)

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JOURNAL: Neurourology and Urodynamics 20 (4): p522-524 2001 2001

MEDIUM: print

CONFERENCE/MEETING: 31st Annual Meeting of the International Continence Society Seoul, South Korea September 18-21, 2001; 20010918

SPONSOR: International Continence Society

ISSN: 0733-2467

DOCUMENT TYPE: Meeting; Meeting Abstract

RECORD TYPE: Citation

LANGUAGE: English

DESCRIPTORS:

MAJOR CONCEPTS: Urology--Human Medicine, Medical Sciences; Pharmacognosy  
--Pharmacology

BIOSYSTEMATIC NAMES: Endospore-forming Gram-Positives--Eubacteria,  
Bacteria, Microorganisms; Hominidae--Primates, Mammalia, Vertebrata,  
Chordata, Animalia

ORGANISMS: Clostridium botulinum (Endospore-forming Gram-Positives)--  
medical agent; human (Hominidae)--patient

ORGANISMS: PARTS ETC: bladder--excretory system, capacity, pressure;  
detrusor muscle--muscular system

COMMON TAXONOMIC TERMS: Bacteria; Eubacteria; Microorganisms; Animals;  
Chordates; Humans; Mammals; Primates; Vertebrates

DISEASES: detrusor hyperreflexia --urologic disease

CHEMICALS & BIOCHEMICALS: botulinum-A toxin --anticholinergic-drug,  
renal-acting-drug, Clostridium botulinum extract, dosage, efficacy,  
neurotoxin , side effects

METHODS & EQUIPMENT: drug treatment--therapeutic method; videodynamics--  
diagnostic method

MISCELLANEOUS TERMS: continence status; hypostenia; quality of life;  
Meeting Abstract; Meeting Abstract

CONCEPT CODES:

00520 General biology - Symposia, transactions and proceedings

15506 Urinary system - Pathology

31000 Physiology and biochemistry of bacteria

36002 Medical and clinical microbiology - Bacteriology

54000 Pharmacognosy and pharmaceutical botany

BIOSYSTEMATIC CODES:

07810 Endospore-forming Gram-Positives

86215 Hominidae

35/9/2 (Item 1 from file: 73)

DIALOG(R) File 73:EMBASE

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07796755 EMBASE No: 1999279042

Botulinum toxin in the treatment of neurological disorders of the  
autonomic nervous system

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Germany

Archives of Neurology ( ARCH. NEUROL. ) (United States) 1999, 56/8  
(914-916)

CODEN: ARNEA ISSN: 0003-9942

DOCUMENT TYPE: Journal; Review

LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

NUMBER OF REFERENCES: 11

Botulinum neurotoxin A (BoNT/A) has become a valuable tool in the treatment of neurological disorders associated with increased muscle tone and has revolutionized the treatment of dystonia and focal spasticity. It acts at cholinergic nerve terminals by cleaving SNAP-25, a protein involved in the fusion of synaptic vesicles with the presynaptic membrane. Cholinergic autonomic parasympathetic and postganglionic sympathetic nerve synapses are also amenable to treatment with botulinum toxin .

DRUG DESCRIPTORS:

\*botulinum toxin --drug dose--do; \*botulinum toxin --drug therapy--dt; \*botulinum toxin --pharmacokinetics--pk; \*synaptosomal associated protein 25 neutralizing antibody

MEDICAL DESCRIPTORS:

\*autonomic nervous system; \*dystonia--drug therapy--dt; \*spasticity--drug therapy--dt muscle tone; cholinergic nerve; nerve ending; synapse vesicle; presynaptic membrane; sweating; lacrimal gland; salivary gland; bladder dysfunction --drug therapy--dt; treatment indication; drug efficacy; myotomy; hypersalivation--drug therapy--dt; detrusor dyssynergia --drug therapy--dt ; constipation--drug therapy--dt; human; major clinical study; review; priority journal

CAS REGISTRY NO.: 187759-31-5 (synaptosomal associated protein 25)

SECTION HEADINGS:

008 Neurology and Neurosurgery

037 Drug Literature Index

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L12: Entry 58 of 64

File: USPT

Oct 8, 2002

DOCUMENT-IDENTIFIER: US 6462044 B2

TITLE: Nitrosated and nitrosylated phosphodiesterase inhibitors, compositions and methods of use

## CLAIMS:

9. A method of claim 8, wherein the disease induced by the increased metabolism of cyclic guanosine 3',5'-monophosphate is hypertension, pulmonary hypertension, congestive heart failure, renal failure, myocardial infarction, stable, unstable and variant (Prinzmetal) angina, atherosclerosis, cardiac edema, renal insufficiency, nephrotic edema, hepatic edema, stroke, asthma, bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, dementia immunodeficiency, premature labor, ~~dysmenorrhoea~~, benign prostatic hyperplasia, bladder outlet obstruction, incontinence, a condition of reduced blood vessel patency, postpercutaneous transluminal coronary angioplasty, peripheral vascular disease, allergic rhinitis, glaucoma, or a disease characterized by a gut motility disorder.

11. The composition of claim 10, wherein the vasoactive agent is a potassium channel activator, a calcium blocker, an .alpha.-blocker, a .beta.-blocker, adenosine, an ergot alkaloid, a vasoactive intestinal peptide, a dopamine agonist, an opioid antagonist, a prostaglandin, an endothelin antagonist or a mixture thereof.

17. A method of claim 16, wherein the disease induced by the increased metabolism of cyclic guanosine 3',5'-monophosphate is hypertension, pulmonary hypertension, congestive heart failure, renal failure, myocardial infarction, stable, unstable and variant (Prinzmetal) angina, atherosclerosis, cardiac edema, renal insufficiency, nephrotic edema, hepatic edema, stroke, asthma, bronchitis, chronic obstructive pulmonary disease, dementia immunodeficiency, premature labor, dysmenorrhoea, benign prostatic hyperplasia, bladder outlet obstruction, incontinence, a condition of reduced blood vessel patency, postpercutaneous transluminal coronary angioplasty, peripheral vascular disease, allergic rhinitis, cystic fibrosis, glaucoma, or a disease characterized by a gut motility disorder.

32. The method of claim 31, wherein the disease induced by the increased metabolism of cyclic guanosine 3',5'-monophosphate is hypertension, pulmonary hypertension, congestive heart failure, renal failure, myocardial infarction, stable, unstable and variant (Prinzmetal) angina, atherosclerosis, cardiac edema, renal insufficiency, nephrotic edema, hepatic edema, stroke, asthma, bronchitis, chronic obstructive pulmonary disease, dementia, immunodeficiency, premature labor, dysmenorrhoea, benign prostatic hyperplasia, bladder outlet obstruction, incontinence, a condition of reduced blood vessel patency, postpercutaneous transluminal coronary angioplasty, peripheral vascular disease, allergic rhinitis, glaucoma, cystic fibrosis, or a disease characterized by a gut motility disorder.

34. The composition of claim 33, wherein the vasoactive agent is a potassium channel activator, a calcium blocker, an .alpha.-blocker, a .beta.-blocker, adenosine, an ergot alkaloid, a vasoactive intestinal peptide, a dopamine agonist, an opioid antagonist, a prostaglandin, an endothelin antagonist or a mixture thereof.

40. The method of claim 39, wherein the disease induced by the increased metabolism of cyclic guanosine 3',5'-monophosphate is hypertension, pulmonary hypertension, congestive heart failure, renal failure, myocardial infarction, stable, unstable and variant (Prinzmetal) angina, atherosclerosis, cardiac edema, renal insufficiency, nephrotic edema, hepatic edema, stroke, asthma, bronchitis, chronic obstructive pulmonary disease, dementia, immunodeficiency, premature labor, dysmenorrhoea, benign prostatic hyperplasia, bladder outlet obstruction, incontinence, a condition of reduced blood vessel patency, postpercutaneous transluminal coronary angioplasty, peripheral vascular disease, allergic rhinitis, cystic fibrosis, glaucoma, or a disease characterized by a gut motility disorder.

50. A method for treating renal failure, atherosclerosis, cardiac edema, renal insufficiency, nephrotic edema, hepatic edema, stroke, bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, dementia, immunodeficiency, premature labor, dysmenorrhoea, benign prostatic hyperplasia, bladder outlet obstruction, incontinence, a condition of reduced blood vessel patency, postpercutaneous transluminal coronary angioplasty, peripheral vascular disease, glaucoma, or a disease characterized by a gut motility disorder comprising administering a therapeutically effective amount of at least one phosphodiesterase inhibitor, or a pharmaceutically acceptable salt thereof, having at least one NO.sub.2 group, wherein the at least one NO.sub.2 group is linked to the phosphodiesterase inhibitors through an oxygen atom, a nitrogen atom, or a sulfur atom.

52. The composition of claim 51, wherein the vasoactive agent is a potassium channel activator, a calcium blocker, an .alpha.-blocker, a .beta.-blocker, adenosine, an ergot alkaloid, a vasoactive intestinal peptide, a dopamine agonist, an opioid antagonist, a prostaglandin, an endothelin antagonist or a mixture thereof.

65. The method of claim 8, wherein the composition is administered orally, buccally, parentally, by inhalation, by topical application, or by transdermal application.

66. The method of claim 16, wherein the composition is administered orally, buccally, parentally, by inhalation, by topical application, or by transdermal application.

67. The method of claim 31, wherein the composition is administered orally, buccally, parentally, by inhalation, by topical application, or by transdermal application.

68. The method of claim 39, wherein the composition is administered orally, buccally, parentally, by inhalation, by topical application, or by transdermal application.

69. The method of claim 50, wherein the composition is administered orally, buccally, parentally, by inhalation, by topical application, or by transdermal application.

TITLE: Nitrosated and nitrosylated potassium channel activators, compositions and methods of use

CLAIMS:

7. The method of claim 4, wherein the composition is administered by intracavernosal injection, by transurethral application or topically.
8. The method of claim 7, wherein the composition is administered topically in the form of a cream, a spray, a lotion, a gel, an ointment, an emulsion, a foam, a coating for a condom, or a liposome composition.
9. A method for treating a cardiovascular disorder, a cerebrovascular disorder, hypertension, asthma, baldness, urinary incontinence, epilepsy, a gastrointestinal disorder, or an irritable bowel syndrome in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 3.
11. A The composition of claim 10, wherein the vasoactive agent is a calcium channel blocker, an .alpha.-adrenergic receptor antagonist, a .beta.-blocker, a phosphodiesterase inhibitor, adenosine, an ergot alkaloid, a vasoactive intestinal peptide, a prostaglandin, a dopamine agonist, an opioid antagonist, an endothelin antagonist, a thromboxane inhibitor or a mixture thereof.
15. The method of claim 12, wherein the composition is administered by intracavernosal injection, by transurethral application or topically.
16. The method of claim 15, wherein the composition is administered topically in the form of a cream, a spray, a lotion, a gel, an ointment, an emulsion, a foam, a coating for a condom, or a liposome composition.
17. A method for treating a cardiovascular disorder, a cerebrovascular disorder, hypertension, asthma, baldness, urinary incontinence, epilepsy, a gastrointestinal disorder, or an irritable bowel syndrome in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 10.
29. The method of claim 26, wherein the composition is administered by intracavernosal injection, by transurethral application or topically.
30. The method of claim 29, wherein the composition is administered topically in the form of a cream, a spray, a lotion, a gel, an ointment, an emulsion, a foam, a coating for a condom, or a liposome composition.
31. A method for treating a cardiovascular disorder, a cerebrovascular disorder, hypertension, asthma, baldness, urinary incontinence, epilepsy, a gastrointestinal disorder, or an irritable bowel syndrome in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 18.
33. The composition of claim 32, wherein the vasoactive agent is a calcium channel blocker, an .alpha.-adrenergic receptor antagonist, a .beta.-blocker, a phosphodiesterase inhibitor, adenosine, an ergot alkaloid, a vasoactive intestinal peptide, a prostaglandin, a dopamine agonist, a prostaglandin, an opioid antagonist, an endothelin antagonist, a thromboxane inhibitor or a mixture thereof.

37. The method of claim 34, wherein the composition is administered by intracavernosal injection, by transurethral application or topically.

38. The method of claim 37, wherein the composition is administered topically in the form of a cream, a spray, a lotion, a gel, an ointment, an emulsion, a foam, a coating for a condom, or a liposome composition.

39. A method for treating a cardiovascular disorder, a cerebrovascular disorder, hypertension, asthma, baldness, urinary incontinence, epilepsy, a gastrointestinal disorder, or an irritable bowel syndrome in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 32.

DOCUMENT-IDENTIFIER: US 6706724 B2

**\*\* See image for Certificate of Correction \*\***

TITLE: Substituted aryl compounds as novel cyclooxygenase-2 selective inhibitors, compositions and methods of use

CLAIMS:

15. The composition of claim 5, wherein the therapeutic agent is a steroid, a nonsteroidal antiinflammatory compound, a 5-lipoxygenase inhibitor, a leukotriene B.sub.4 receptor antagonist, a leukotriene A.sub.4 hydrolase inhibitor, a 5-HT agonist, a 3-hydroxy-3-methylbutyryl coenzyme A inhibitor, a H.sub.2 receptor antagonist, an antineoplastic agent, an antiplatelet agent, a thrombin inhibitor, a thromboxane inhibitor, a decongestant, a diuretic, a sedating or non-sedating anti-histamine, an inducible nitric oxide synthase inhibitor, an opioid, an analgesic, a Helicobacter pylori inhibitor, a proton pump inhibitor, an isoprostane inhibitor, or a mixture of two or more thereof.

17. The composition of claim 16, wherein the therapeutic agent is a steroid, a nonsteroidal antiinflammatory compound, a 5-lipoxygenase inhibitor, a leukotriene B.sub.4 receptor antagonist, a leukotriene A.sub.4 hydrolase inhibitor, a 5-HT agonist, a 3-hydroxy-3-methylglutaryl coenzyme A inhibitor, a H.sub.2 receptor antagonist, an antineoplastic agent, an antiplatelet agent, a thrombin inhibitor, a thromboxane inhibitor, a decongestant, a diuretic, a sedating or non-sedating anti-histamine, an inducible nitric oxide synthase inhibitor, an opioid, an analgesic, a Helicobacter pylori inhibitor, a proton pump inhibitor, an isoprostane inhibitor, or a mixture of two or more thereof.

20. The method of claim 19, wherein the disorder resulting from elevated levels of COX-2 is angiogenesis, arthritis, asthma, bronchitis, menstrual cramps, premature labor, tendonitis, bursitis, a skin related condition, neoplasia, inflammation in disease, ophthalmic disorder, pulmonary inflammation, central nervous system disorder, allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis, inflammation, microbial infection, cardiovascular disorder, urinary disorder, urological disorder, endothelial dysfunction, a disorder treated by the preservation of organs and tissues, a disorder treated by inhibition of activation, adhesion and infiltration of neutrophils at the site of inflammation, or a disorder treated by inhibition of platelet aggregation.

30. The method of claim 29, wherein the compound of claim 2 or a pharmaceutically acceptable salt thereof, and the least one of a 3-hydroxy-3-methylglutaryl coenzyme A, an antiplatelet agent, a thrombin inhibitor or a thromboxane inhibitor are administered orally, buccally, topically, by injection, by inhalation, or by transdermal application.

33. The method of claim 32, wherein the disorder resulting from elevated levels of COX-2 is angiogenesis, arthritis, asthma, bronchitis, menstrual cramps, premature labor, tendonitis, bursitis, a skin-related condition, neoplasia, inflammation in disease, ophthalmic disorder, pulmonary inflammation, central nervous system disorder, allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis, inflammation, microbial infection, cardiovascular disorder, urinary disorder, urological disorder, endothelial dysfunction, a disorder treated by the preservation of organs and tissues, a disorder treated by inhibition of activation, adhesion and infiltration of neutrophils at the site of inflammation, or a disorder treated by inhibition of platelet aggregation.

42. The composition of claim 5, wherein the least one compound of claim 1 or a pharmaceutically acceptable salt thereof, the least one compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase and the at least one therapeutic agents are administered orally, buccally, topically,

by injection, by inhalation, or by transdermal application.

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End of Result Set



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L6: Entry 3 of 3

File: USPT

Dec 7, 2004

DOCUMENT-IDENTIFIER: US 6828473 B2

TITLE: Modulation of PDE11A activity

Detailed Description Text (139):

For example, given PDE11A expression in bladder urothelium, it is a candidate as a regulator of nitric oxide (NO)-mediated inhibition of bladder and bladder nerve fiber excitability. This NO-mediated effect is described, e.g., in Ozawa et al., J. Urol. 162: 2211, 1999, Pandita et al., J. Urol. 545-550, 2000, and Burnett et al., Nat. Med. 3: 571-74, 1997. To characterize the role of PDE11A in bladder contractility, the effects of a PDE11A antagonist can be studied in a model of oxyhemoglobin-induced (Pandita, supra) or cyclophosphamide-induced (Ozawa, supra), bladder hyperactivity. Experimental animals (e.g., rats) are administered oxyhemoglobin (intravesically, Sigma Chemical) or cyclophosphamide (intraperitoneally) in combination with a PDE11A antagonist dissolved, e.g., in DMSO and diluted by an appropriate buffer. The PDE11A antagonist is administered by an appropriate route (e.g., intravesically, intraperitoneally, or intravenously).

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L6: Entry 1 of 3

File: PGPB

Dec 11, 2003

DOCUMENT-IDENTIFIER: US 20030229002 A1

TITLE: Use of agents that modulate PDE11A activity

Detail Description Paragraph:

[0329] For example, given PDE11A expression in bladder urothelium, it is a candidate as a regulator of nitric oxide (NO)-mediated inhibition of bladder and bladder nerve fiber excitability. This NO-mediated effect is described, e.g., in Ozawa et al., J. Urol. 162: 2211, 1999, Pandita et al., J. Urol. 545-550, 2000, and Burnett et al., Nat. Med. 3: 571-74, 1997. To characterize the role of PDE11A in bladder contractility, the effects of a PDE11A antagonist can be studied in a model of oxyhemoglobin-induced (Pandita, supra) or cyclophosphamide-induced (Ozawa, supra), bladder hyperactivity. Experimental animals (e.g., rats) are administered oxyhemoglobin (intravesically, Sigma Chemical) or cyclophosphamide (intraperitoneally) in combination with a PDE11A antagonist dissolved, e.g., in DMSO and diluted by an appropriate buffer. The PDE11A antagonist is administered by an appropriate route (e.g., intravesically, intraperitoneally, or intravenously).

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L6: Entry 2 of 3

File: PGPB

Mar 27, 2003

DOCUMENT-IDENTIFIER: US 20030061625 A1

TITLE: Modulation of PDE11A activity

Detail Description Paragraph:

[0210] For example, given PDE11A expression in bladder urothelium, it is a candidate as a regulator of nitric oxide (NO)-mediated inhibition of bladder and bladder nerve fiber excitability. This NO-mediated effect is described, e.g., in Ozawa et al., J. Urol. 162: 2211, 1999, Pandita et al., J. Urol. 545-550, 2000, and Burnett et al., Nat. Med. 3: 571-74, 1997. To characterize the role of PDE11A in bladder contractility, the effects of a PDE11A antagonist can be studied in a model of oxyhemoglobin-induced (Pandita, supra) or cyclophosphamide-induced (Ozawa, supra), bladder hyperactivity. Experimental animals (e.g., rats) are administered oxyhemoglobin (intravesically, Sigma Chemical) or cyclophosphamide (intraperitoneally) in combination with a PDE11A antagonist dissolved, e.g., in DMSO and diluted by an appropriate buffer. The PDE11A antagonist is administered by an appropriate route (e.g., intravesically, intraperitoneally, or intravenously).

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DOCUMENT-IDENTIFIER: US 20040077706 A1

TITLE: Ligands for monoamine receptors and transporters, and methods of use thereof

CLAIMS:

128. A method of modulating the activity of a dopamine, serotonin, or norepinephrine receptor or transporter in a mammal, comprising the step of: administering to said mammal a therapeutically effective amount of a compound of claim 1, 37, 66, or 95.

138. The method of claim 128, wherein said compound is administered topically.

143. A method of modulating the activity of a dopamine receptor or transporter in a mammal, comprising the step of: administering to said mammal a therapeutically effective amount of a compound of claim 1, 37, 66, or 95.

153. The method of claim 143, wherein said compound is administered topically.

158. A method of treating a mammal suffering from addiction, anxiety, depression, sexual dysfunction, hypertension, migraine, Alzheimer's disease, obesity, emesis, psychosis, analgesia, schizophrenia, Parkinson's disease, restless leg syndrome, sleeping disorders, attention deficit hyperactivity disorder, irritable bowel syndrome, premature ejaculation, menstrual dysphoria syndrome, urinary incontinence, inflammatory pain, neuropathic pain, Lesche-Nyhan disease, Wilson's disease, or Tourette's syndrome, comprising the step of: administering to said mammal a therapeutically effective amount of a compound of claim 1, 37, 66, or 95.

168. The method of claim 158, wherein said compound is administered topically.

DOCUMENT-IDENTIFIER: US 20030216420 A1

TITLE: Pharmaceutical composition for treating fecal incontinence and anal itch

CLAIMS:

1. A method for the treatment of fecal incontinence or anal itch comprising topically administering in and/or around the anal canal of a patient a physiologically active agent selected from the group consisting of a adrenergic agonists, nitric oxide synthase inhibitors, prostaglandin F.sub.2.alpha., dopamine, morphine, beta-blockers, and 5-Hydroxytryptamine.
2. The method according to claim 1 wherein the active agent is selected from the group consisting of .alpha. adrenergic agonists, nitric oxide synthase inhibitors and prostaglandin F.sub.2.alpha..
8. A rectally administrable topically acting pharmaceutical composition for local application in the treatment of fecal incontinence or anal itch comprising at least one active agent selected from the group consisting of a adrenergic agonists, nitric oxide synthase inhibitors, prostaglandin F.sub.2.alpha., dopamine, morphine, beta-blockers, and 5-Hydroxytryptamine together with a pharmacologically acceptable carrier, provided that the composition does not include a xanthine when the active agent is phenylephrine.
9. A topical composition for local application in the treatment of fecal incontinence or anal itch comprising N.sup.G-nitro-L-arginine methyl ester (L-NAME) together with a pharmacologically acceptable carrier.
10. A topical composition for local application in the treatment of fecal incontinence or anal itch comprising phenylephrine in an amount of at least 10%.
12. A method for the treatment of fecal incontinence comprising topically administering in and/or around the anal canal of a patient, an internal anal sphincter pressure increasing amount of a physiologically active agent comprising an .alpha. adrenergic agonist.
19. A method for the treatment of fecal incontinence comprising topically administering in and/or around the anal canal of a patient an internal anal sphincter pressure increasing amount of a physiologically active agent selected from the group consisting of phenylephrine, nor-adrenalin and methoxamine and pharmacologically acceptable salts thereof.
20. A method for the treatment of fecal incontinence comprising topically administering in and/or around the anal canal of a patient, an internal anal sphincter pressure increasing amount of phenylephrine or a pharmacologically acceptable salt thereof.
21. A method for the treatment of fecal incontinence comprising topically administering in and/or around the anal canal of a patient, a topical composition comprising at least 5% w/w of phenylephrine or a pharmacologically acceptable salt thereof.
22. A method for the treatment of fecal incontinence comprising topically administering in and/or around the anal canal of a patient, a topical composition comprising as the sole physiologically active agent a fecal incontinence treating amount of phenylephrine or a pharmacologically acceptable salt thereof.

DOCUMENT-IDENTIFIER: US 20030105071 A1

TITLE: Thiazole and other heterocyclic ligands for mammalian dopamine, muscarinic and serotonin receptors and transporters, and methods of use thereof

CLAIMS:

59. A method of modulating the activity of a dopamine, muscarinic or serotonin receptor or transporter in a mammal, comprising the step of: administering to said mammal a therapeutically effective amount of a compound of claim 1, 17, 25, or 37.

70. The method of claim 59, wherein said compound is administered topically.

75. A method of modulating the activity of a dopamine, muscarinic or serotonin receptor in a mammal, comprising the step of: administering to said mammal a therapeutically effective amount of a compound of claim 1, 17, 25, or 37.

86. The method of claim 75, wherein said compound is administered topically.

91. A method of treating a mammal suffering from addiction, anxiety, depression, sexual dysfunction, hypertension, migraine, Alzheimer's disease, obesity, emesis, psychosis, analgesia, schizophrenia, Parkinson's disease, restless leg syndrome, sleeping disorders, attention deficit hyperactivity disorder, irritable bowel syndrome, premature ejaculation, menstrual dysphoria syndrome, urinary incontinence, inflammatory pain, neuropathic pain, Lesche-Nyhan disease, Wilson's disease, Tourette's syndrome, psychiatric disorders, stroke, senile dementia, peptic ulcers, pulmonary obstruction disorders, or asthma, comprising the step of: administering to said mammal a therapeutically effective amount of a compound of claim 1, 17, 25, or 37.

101. The method of claim 91, wherein said compound is administered topically.



US 20040229920A1

(19) **United States**(12) **Patent Application Publication** (10) **Pub. No.: US 2004/0229920 A1****Garvey et al.**(43) **Pub. Date: Nov. 18, 2004**(54) **NITROSATED AND NITROSYLATED  
POTASSIUM CHANNEL ACTIVATORS,  
COMPOSITIONS AND METHODS OF USE**(52) **U.S. Cl. .... 514/355; 546/315**(76) **Inventors: David S. Garvey, Dover, MA (US);  
Inigo Saenz de Tejada, Madrid (ES)**(57) **ABSTRACT**

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The present invention describes novel nitrosated and/or nitrosylated potassium channel activators, and novel compositions comprising at least one nitrosated and/or nitrosylated potassium channel activator, and, optionally, at least one compound that donates, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase and/or at least one vasoactive agent. The present invention also provides novel compositions comprising at least one potassium channel activator, and at least one compound that donates, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase and/or at least one vasoactive agent. The present invention also provides methods for treating or preventing sexual dysfunctions in males and females, for enhancing sexual responses in males and females, and for treating or preventing cardiovascular disorders, cerebrovascular disorders, hypertension, asthma, baldness, urinary incontinence, epilepsy, sleep disorders, gastrointestinal disorders, migraines, irritable bowel syndrome and sensitive skin.

(21) **Appl. No.: 10/757,576**(22) **Filed: Jan. 15, 2004****Related U.S. Application Data**

(63) Continuation of application No. 10/154,916, filed on May 28, 2002, now Pat. No. 6,693,122, which is a continuation of application No. 09/570,727, filed on May 12, 2000, now Pat. No. 6,417,207.

(60) Provisional application No. 60/133,888, filed on May 12, 1999.

**Publication Classification**(51) **Int. Cl.<sup>7</sup> ..... C07D 213/46; A61K 31/44**

First Hit

L12: Entry 10 of 64

File: PGPB

Nov 18, 2004

DOCUMENT-IDENTIFIER: US 20040229920 A1

TITLE: Nitrosated and nitrosylated potassium channel activators, compositions and methods of use

## CLAIMS:

12. The method of claim 9, wherein the composition is administered by intracavernosal injection, by transurethral application or topically.

13. The method of claim 12, wherein the composition is administered topically in the form of a cream, a spray, a lotion, a gel, an ointment, an emulsion, a foam, a coating for a condom, or a liposome composition.

14. A method for treating a cardiovascular disorder, a cerebrovascular disorder, hypertension, asthma, baldness, urinary incontinence, epilepsy, a sleep disorder, a gastrointestinal disorder, a migraine, an irritable bowel syndrome or sensitive skin in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 8.

16. The composition of claim 15, wherein the vasoactive agent is a calcium channel blocker, an .alpha.-adrenergic receptor antagonist, a .beta.-blocker, a phosphodiesterase inhibitor, adenosine, an ergot alkaloid, a vasoactive intestinal peptide, a prostaglandin, a dopamine agonist, an opioid antagonist, an endothelin antagonist, a thromboxane inhibitor or a mixture thereof.

20. The method of claim 17, wherein the composition is administered by intracavernosal injection, by transurethral application or topically.

21. The method of claim 20, wherein the composition is administered topically in the form of a cream, a spray, a lotion, a gel, an ointment, an emulsion, a foam, a coating for a condom, or a liposome composition.

22. A method for treating a cardiovascular disorder, a cerebrovascular disorder, hypertension, asthma, baldness, urinary incontinence, epilepsy, a sleep disorder, a gastrointestinal disorder, a migraine, an irritable bowel syndrome or sensitive skin in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 15.

34. The method of claim 31, wherein the composition is administered by intracavernosal injection, by transurethral application or topically.

35. The method of claim 34, wherein the composition is administered topically in the form of a cream, a spray, a lotion, a gel, an ointment, an emulsion, a foam, a coating for a condom, or a liposome composition.

36. A method for treating a cardiovascular disorder, a cerebrovascular disorder, hypertension, asthma, baldness, urinary incontinence, epilepsy, a sleep disorder, a gastrointestinal disorder, a migraine, an irritable bowel syndrome or sensitive skin in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 23.

38. The composition of claim 37, wherein the vasoactive agent is a calcium channel blocker, an .alpha.-adrenergic receptor antagonist, a .beta.-blocker, a phosphodiesterase inhibitor, adenosine, an ergot alkaloid, a vasoactive intestinal peptide, a prostaglandin, a dopamine agonist, a prostaglandin, an opioid antagonist, an endothelin antagonist, a thromboxane inhibitor or a mixture thereof.

42. The method of claim 39, wherein the composition is administered by intracavernosal injection, by transurethral application or topically.

43. The method of claim 42, wherein the composition is administered topically in the form of a cream, a spray, a lotion, a gel, an ointment, an emulsion, a foam, a coating for a condom, or a liposome composition.

44. A method for treating a cardiovascular disorder, a cerebrovascular disorder, hypertension, asthma, baldness, urinary incontinence, epilepsy, a sleep disorder, a gastrointestinal disorder, a migraine, an irritable bowel syndrome or sensitive skin in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 37.

59. The method of claim 56, wherein the composition is administered by intracavernosal injection, by transurethral application or topically.

60. The method of claim 59, wherein the composition is administered topically in the form of a cream, a spray, a lotion, a gel, an ointment, an emulsion, a foam, a coating for a condom, or a liposome composition.

61. A method for treating a cardiovascular disorder, a cerebrovascular disorder, hypertension, asthma, baldness, urinary incontinence, epilepsy, a sleep disorder, a gastrointestinal disorder, a migraine, an irritable bowel syndrome or sensitive skin in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 45.

63. The composition of claim 62, wherein the vasoactive agent is a calcium channel blocker, an .alpha.-adrenergic receptor antagonist, a .beta.-blocker, a phosphodiesterase inhibitor, adenosine, an ergot alkaloid, a vasoactive intestinal peptide, a prostaglandin, a dopamine agonist, an opioid antagonist, an endothelin antagonist, a thromboxane inhibitor or a mixture thereof.

67. The method of claim 62, wherein the composition is administered by intracavernosal injection, by transurethral application or topically.

68. The method of claim 67, wherein the composition is administered topically in the form of a cream, a spray, a lotion, a gel, an ointment, an emulsion, a foam, a coating for a condom, or a liposome composition.

69. A method for treating a cardiovascular disorder, a cerebrovascular disorder, hypertension, asthma, baldness, urinary incontinence, epilepsy, a sleep disorder, a gastrointestinal disorder, a migraine, an irritable bowel syndrome or sensitive skin in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 62.

74. The composition of claim 68, wherein the vasoactive agent is a calcium channel blocker, an .alpha.-adrenergic receptor antagonist, a .beta.-blocker, a phosphodiesterase inhibitor, adenosine, an ergot alkaloid, a vasoactive intestinal peptide, a prostaglandin, a dopamine agonist, an opioid antagonist, an endothelin antagonist, a thromboxane inhibitor or a mixture thereof.

78. The method of claim 75, wherein the composition is administered by intracavernosal injection, by transurethral application or topically.

79. The method of claim 78, wherein the composition is administered topically in the form of a cream, a spray, a lotion, a gel, an ointment, an emulsion, a foam, a coating for a condom, or a liposome composition.

80. A method for treating a cardiovascular disorder, a cerebrovascular disorder, hypertension, asthma, baldness, urinary incontinence, epilepsy, a sleep disorder, a gastrointestinal disorder, a migraine, an irritable bowel syndrome or sensitive skin in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 70.





US 20040235913A1

(19) **United States**(12) **Patent Application Publication** (10) Pub. No.: **US 2004/0235913 A1**

Cuny et al.

(43) Pub. Date: **Nov. 25, 2004**

(54) **THIAZOLE AND OTHER HETEROCYCLIC  
LIGANDS FOR MAMMALIAN DOPAMINE,  
MUSCARINIC AND SEROTONIN  
RECEPTORS AND TRANSPORTERS, AND  
METHODS OF USE THEREOF**

**Publication Classification**

(51) Int. Cl.<sup>7</sup> ..... **A61K 31/426**  
(52) U.S. Cl. .... **514/365**

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(21) Appl. No.: **10/786,612**(22) Filed: **Feb. 25, 2004****Related U.S. Application Data**

(62) Division of application No. 10/123,089, filed on Apr. 12, 2002, now Pat. No. 6,699,866.

(60) Provisional application No. 60/284,159, filed on Apr. 17, 2001. Provisional application No. 60/313,648, filed on Aug. 20, 2001.

(57) **ABSTRACT**

One aspect of the present invention relates to novel heterocyclic compounds. A second aspect of the present invention relates to the use of the novel heterocyclic compounds as ligands for various mammalian cellular receptors, including G-protein coupled receptors. A third aspect of the present invention relates to the use of the novel heterocyclic compounds as ligands for mammalian dopamine, muscarinic or serotonin receptors or transporters. Another aspect of the present invention relates to the use of the novel heterocyclic compounds as ligands for mammalian dopamine, muscarinic or serotonin receptors. The compounds of the present invention will also find use in the treatment of numerous ailments, conditions and diseases which afflict mammals, including but not limited to addiction, anxiety, depression, sexual dysfunction, hypertension, migraine, Alzheimer's disease, obesity, emesis, psychosis, analgesia, schizophrenia, Parkinson's disease, restless leg syndrome, sleeping disorders, attention deficit hyperactivity disorder, irritable bowel syndrome, premature ejaculation, menstrual dysphoria syndrome, urinary incontinence, inflammatory pain, neuropathic pain, Lesche-Nyhan disease, Wilson's disease, Tourette's syndrome, psychiatric disorders, stroke, senile dementia, peptic ulcers, pulmonary obstruction disorders, and asthma.

DOCUMENT-IDENTIFIER: US 20040235913 A1

TITLE: Thiazole and other heterocyclic ligands for mammalian dopamine, muscarinic and serotonin receptors and transporters, and methods of use thereof

CLAIMS:

59. A method of modulating the activity of a dopamine, muscarinic or serotonin receptor or transporter in a mammal, comprising the step of: administering to said mammal a therapeutically effective amount of a compound of claim 1, 17, 25, or 37.

70. The method of claim 59, wherein said compound is administered topically.

75. A method of modulating the activity of a dopamine, muscarinic or serotonin receptor in a mammal, comprising the step of: administering to said mammal a therapeutically effective amount of a compound of claim 1, 17, 25, or 37.

86. The method of claim 75, wherein said compound is administered topically.

91. A method of treating a mammal suffering from addiction, anxiety, depression, sexual dysfunction, hypertension, migraine, Alzheimer's disease, obesity, emesis, psychosis, analgesia, schizophrenia, Parkinson's disease, restless leg syndrome, sleeping disorders, attention deficit hyperactivity disorder, irritable bowel syndrome, premature ejaculation, menstrual dysphoria syndrome, urinary incontinence, inflammatory pain, neuropathic pain, Lesche-Nyhan disease, Wilson's disease, Tourette's syndrome, psychiatric disorders, stroke, senile dementia, peptic ulcers, pulmonary obstruction disorders, or asthma, comprising the step of: administering to said mammal a therapeutically effective amount of a compound of claim 1, 17, 25, or 37.

101. The method of claim 91, wherein said compound is administered topically.



US 20050228049A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2005/0228049 A1**

**Thor et al.**

(43) **Pub. Date: Oct. 13, 2005**

(54) **METHODS FOR DECREASING DETRUSOR**

(75) **Inventors:** Karl Bruce Thor, Morrisville, NC (US); Edward C. Burgard, Chapel Hill, NC (US); Matthew Oliver Fraser, Apex, NC (US)

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(60) **Provisional application No. 60/435,021, filed on Dec. 20, 2002. Provisional application No. 60/486,057, filed on Jul. 10, 2003. Provisional application No. 60/525,623, filed on Nov. 26, 2003.**

**Publication Classification**

(51) **Int. Cl.<sup>7</sup> ..... A61K 31/195**  
(52) **U.S. Cl. .... 514/561**

(73) **Assignee:** Dynogen Pharmaceuticals, Inc., Waltham, MA

(21) **Appl. No.: 11/136,183**

(22) **Filed: May 24, 2005**

**Related U.S. Application Data**

(63) **Continuation of application No. 10/741,360, filed on Dec. 19, 2003.**

(57) **ABSTRACT**

A method is provided for treatment of non-painful bladder disorders, particularly non-painful overactive bladder without loss of urine. The method comprises administration of an  $\alpha_2\delta$  subunit calcium channel modulator, including gabapentin, pregabalin, GABA analogs, fused bicyclic or tricyclic amino acid analogs of gabapentin, amino acid compounds, and other compounds that interact with the  $\alpha_2\delta$  calcium channel subunit.

DOCUMENT-IDENTIFIER: US 20050059665 A1

TITLE: Substituted aryl compounds as novel cyclooxygenase-2 selective inhibitors, compositions and methods of use

CLAIMS:

5. The composition of claim 4, wherein the therapeutic agent is a steroid, a nonsteroidal antiinflammatory compound, a 5-lipoxygenase inhibitor, a leukotriene B.sub.4 receptor antagonist, a leukotriene A.sub.4 hydrolase inhibitor, a 5-HT agonist, a 3-hydroxy-3-methylglutaryl coenzyme A inhibitor, a H.sub.2 receptor antagonist, an antineoplastic agent, an antiplatelet agent, a thrombin inhibitor, a thromboxane inhibitor, a decongestant, a diuretic, a sedating or non-sedating anti-histamine, an inducible nitric oxide synthase inhibitor, an opioid, an analgesic, a Helicobacter pylori inhibitor, a proton pump inhibitor, an isoprostane inhibitor, or a mixture of two or more thereof.
8. The method of claim 7, wherein the disorder resulting from elevated levels of COX-2 is angiogenesis, arthritis, asthma, bronchitis, menstrual cramps, premature labor, tendonitis, bursitis, a skin-related condition, neoplasia, inflammation in disease, ophthalmic disorder, pulmonary inflammation, central nervous system disorder, allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis, inflammation, microbial infection, cardiovascular disorder, urinary disorder, urological disorder, endothelial dysfunction, a disorder treated by the preservation of organs and tissues, a disorder treated by inhibition of activation, adhesion and infiltration of neutrophils at the site of inflammation, or a disorder treated by inhibition of platelet aggregation.
17. The composition of claim 1, wherein the least one compound of Formula (I) or a pharmaceutically acceptable salt thereof, and, the at least one compound selected from isosorbide dinitrate, isosorbide mononitrate, clonitrate, erythrityl tetranitrate, mannitol hexanitrate, nitroglycerin, pentaerythritoltetranitrate, pentrinitrol, propatylnitrate and organic nitrates with a sulfhydryl-containing amino are administered orally, buccally, topically, by injection, by inhalation, or by transdermal application.



US 20040209870A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2004/0209870 A1

Ennis et al.

(43) Pub. Date: Oct. 21, 2004

(54) NOVEL  
2,3,4,5-TETRAHYDRO-1H-[1,4]DIAZEPINO-  
[1,7-A]INDOLE COMPOUNDS(76) Inventors: Michael Dalton Ennis, Chesterfield,  
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(21) Appl. No.: 10/761,070

(22) Filed: Jan. 20, 2004

## Related U.S. Application Data

(62) Division of application No. 09/803,242, filed on Mar.  
8, 2001, now Pat. No. 6,734,301.(60) Provisional application No. 60/189,103, filed on Mar.  
14, 2000.

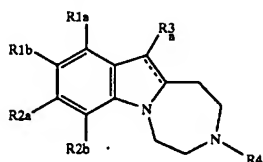
## Publication Classification

(51) Int. Cl.<sup>7</sup> ..... A61K 31/551; C07D 487/12

(52) U.S. Cl. .... 514/220; 540/558

## (57) ABSTRACT

A compound of formula I:



where a is a single bond or double bond, and where

R1a, R1b, R2a and R2b are each independently

(a) H, Cl, Br, I, F, CN, CF<sub>3</sub>, OCF<sub>3</sub>, OR<sub>5</sub>,  
CONR<sub>5</sub>R<sub>6</sub>COR<sub>5</sub>, CO<sub>2</sub>R<sub>5</sub>, Y(CH<sub>2</sub>)<sub>m</sub>XR<sub>5</sub> or  
YC(O)(CH<sub>2</sub>)<sub>m</sub>XR<sub>5</sub>, where m=0-3, Y=CH<sub>2</sub>, S, O, or  
NR<sub>6</sub>, X=CH<sub>2</sub>, S, O, NR<sub>6</sub>;(b) (CH<sub>2</sub>)<sub>p</sub>Ar where p=0-3 and Ar is aryl or heteroaryl  
optionally substituted with one or more of the fol-  
lowing: H, halogen, CN, NO<sub>2</sub>, OR<sub>7</sub>, CF<sub>3</sub>, OCF<sub>3</sub>,  
SR<sub>7</sub>, SO<sub>2</sub>R<sub>7</sub>, SO<sub>2</sub>NR<sub>7</sub>R<sub>8</sub>, NR<sub>7</sub>R<sub>8</sub>, CONR<sub>7</sub>R<sub>8</sub>,  
NR<sub>7</sub>COR<sub>8</sub>, NR<sub>7</sub>CONR<sub>8</sub>R<sub>9</sub>, CO<sub>2</sub>R<sub>7</sub>, COR<sub>7</sub>, or R<sub>7</sub>;  
or(c) linear or branched C<sub>1</sub>-C<sub>8</sub> alkyl, linear or branched  
C<sub>2</sub>-C<sub>8</sub> alkenyl, linear or branched C<sub>2</sub>-C<sub>8</sub> alkynyl,  
C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkenyl, or C<sub>3</sub>-C<sub>8</sub>  
cycloalkynyl; wherein any of these groups may be  
optionally substituted with one or more of the fol-lowing: halogen, CN, NO<sub>2</sub>, COR<sub>7</sub>, OR<sub>7</sub>, NR<sub>7</sub>R<sub>8</sub>,  
SR<sub>7</sub>, CO<sub>2</sub>R<sub>7</sub>, CONR<sub>7</sub>R<sub>8</sub> or NR<sub>7</sub>COR<sub>8</sub>; and whereR<sub>3</sub> is(a) H, Cl, Br, I, F, CN, CF<sub>3</sub>, OCF<sub>3</sub>, alkyl, Ar, OR<sub>5</sub>, SR<sub>5</sub>,  
CHO, CONR<sub>5</sub>R<sub>6</sub>, COR<sub>5</sub>, CO<sub>2</sub>R<sub>5</sub>, (Y)<sub>o</sub>(CH<sub>2</sub>)<sub>n</sub>XR<sub>5</sub>,  
C(O)C(O)XR<sub>5</sub>, (Y)<sub>o</sub>(CH<sub>2</sub>)<sub>n</sub>C(O)XR<sub>5</sub>,  
C(O)(CH<sub>2</sub>)<sub>n</sub>XR<sub>5</sub>, (Y)<sub>o</sub>(CH<sub>2</sub>)<sub>n</sub>N(R<sub>6</sub>)C(O)R<sub>5</sub>,  
(Y)<sub>o</sub>(CH<sub>2</sub>)<sub>n</sub>N(R<sub>6</sub>)S(O)<sub>2</sub>R<sub>5</sub>,  
(Y)<sub>o</sub>(CH<sub>2</sub>)<sub>n</sub>N(R<sub>6</sub>)C(O)OR<sub>5</sub>,  
(Y)<sub>o</sub>(CH<sub>2</sub>)<sub>n</sub>N(R<sub>6</sub>)C(O)NR<sub>5</sub>R<sub>6</sub> where o=0 or 1, n=0-  
3, X=CH<sub>2</sub>, S, O, or NR<sub>6</sub> and Y=CH<sub>2</sub>, S, O or NR<sub>6</sub>,  
where Ar is aryl or heteroaryl optionally substituted  
with one or more of the following: H, halogen, CN,  
NO<sub>2</sub>, OR<sub>7</sub>, CF<sub>3</sub>, OCF<sub>3</sub>, SR<sub>7</sub>, SO<sub>2</sub>R<sub>7</sub>, SO<sub>2</sub>NR<sub>7</sub>R<sub>8</sub>,  
NR<sub>7</sub>R<sub>8</sub>, CONR<sub>7</sub>R<sub>8</sub>, NR<sub>7</sub>COR<sub>8</sub>, NR<sub>7</sub>CONR<sub>8</sub>R<sub>9</sub>,  
CO<sub>2</sub>R<sub>7</sub>, COR<sub>7</sub>, or R<sub>7</sub>; or(b) linear or branched C<sub>1</sub>-C<sub>8</sub> alkyl, linear or branched  
C<sub>2</sub>-C<sub>8</sub> alkenyl, linear or branched C<sub>2</sub>-C<sub>8</sub> alkynyl,  
C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkenyl, or C<sub>3</sub>-C<sub>8</sub>  
cycloalkynyl; wherein any of these groups may be  
optionally substituted with one or more of the fol-  
lowing: halogen, CN, NO<sub>2</sub>, COR<sub>10</sub>, OR<sub>10</sub>,  
NR<sub>10</sub>R<sub>8</sub>, SR<sub>10</sub>, CO<sub>2</sub>R<sub>10</sub>, CONR<sub>10</sub>R<sub>8</sub> or  
NR<sub>10</sub>COR<sub>8</sub>; and whereR<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are each independently(a) H, linear or branched C<sub>1</sub>-C<sub>8</sub> alkyl, linear or  
branched C<sub>2</sub>-C<sub>8</sub> alkenyl, linear or branched C<sub>2</sub>-C<sub>8</sub>  
alkynyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkenyl, or  
C<sub>3</sub>-C<sub>8</sub> cycloalkynyl; wherein any of these groups  
other than H may be optionally substituted with one  
or more of the following: halogen, CN, NO<sub>2</sub>,  
COR<sub>10</sub>, OR<sub>10</sub>, NR<sub>10</sub>R<sub>11</sub>, SR<sub>10</sub>, CO<sub>2</sub>R<sub>10</sub>,  
CONR<sub>10</sub>R<sub>11</sub> or NR<sub>10</sub>COR<sub>11</sub>; or where R<sub>5</sub> and R<sub>6</sub>  
are linked to form a 3 to 8 member ring; or(b) (CH<sub>2</sub>)<sub>p</sub>Ar where p=0-3 and Ar is aryl or heteroaryl  
optionally substituted with one or more of the fol-  
lowing: H, halogen, CN, NO<sub>2</sub>, OR<sub>7</sub>, CF<sub>3</sub>, OCF<sub>3</sub>,  
SR<sub>7</sub>, SO<sub>2</sub>R<sub>7</sub>, SO<sub>2</sub>NR<sub>7</sub>R<sub>8</sub>, NR<sub>7</sub>R<sub>8</sub>, CONR<sub>7</sub>R<sub>8</sub>,  
NR<sub>7</sub>COR<sub>8</sub>, NR<sub>7</sub>CONR<sub>8</sub>R<sub>9</sub>, CO<sub>2</sub>R<sub>7</sub>, COR<sub>7</sub>, or R<sub>7</sub>;  
and whereR<sub>7</sub>, R<sub>8</sub>, and R<sub>9</sub> are each independently(a) H, linear or branched C<sub>1</sub>-C<sub>8</sub> alkyl, linear or  
branched C<sub>2</sub>-C<sub>8</sub> alkenyl, linear or branched C<sub>2</sub>-C<sub>8</sub>  
alkynyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkenyl, or  
C<sub>3</sub>-C<sub>8</sub> cycloalkynyl groups, wherein any of these  
groups other than H may be optionally substituted  
with halogen, CN, NO<sub>2</sub>, COR<sub>10</sub>, OR<sub>10</sub>, NR<sub>10</sub>R<sub>11</sub>,  
SR<sub>10</sub>, CO<sub>2</sub>R<sub>10</sub>, CONR<sub>10</sub>R<sub>11</sub>, NR<sub>10</sub>COR<sub>11</sub>,  
NR<sub>10</sub>CONR<sub>11</sub>R<sub>12</sub>, or where R<sub>7</sub>, R<sub>8</sub>, or R<sub>9</sub> are  
linked to form a ring; or(b) (CH<sub>2</sub>)<sub>p</sub>Ar where p=0-3 and Ar is aryl or heteroaryl  
optionally substituted with one or more of the fol-  
lowing: H, halogen, CN, NO<sub>2</sub>, OR<sub>10</sub>, CF<sub>3</sub>, OCF<sub>3</sub>,  
SR<sub>10</sub>, SO<sub>2</sub>R<sub>10</sub>, SO<sub>2</sub>NR<sub>10</sub>R<sub>11</sub>, NR<sub>10</sub>R<sub>11</sub>,  
CONR<sub>10</sub>R<sub>11</sub>, NR<sub>10</sub>COR<sub>11</sub>, NR<sub>10</sub>CONR<sub>11</sub>R<sub>12</sub>,  
CO<sub>2</sub>R<sub>10</sub>, COR<sub>10</sub>, or R<sub>10</sub>; and whereR<sub>10</sub>, R<sub>11</sub> and R<sub>12</sub> are each independently H, linear or  
branched C<sub>1</sub>-C<sub>8</sub> alkyl, linear or branched C<sub>2</sub>-C<sub>8</sub>  
alkenyl, linear or branched C<sub>2</sub>-C<sub>8</sub> alkynyl, C<sub>3</sub>-C<sub>8</sub>  
cycloalkenyl, or C<sub>3</sub>-C<sub>8</sub> cycloalkynyl;or a stereoisomer or pharmaceutically acceptable salt  
thereof.

DOCUMENT-IDENTIFIER: US 20040209870 A1

TITLE: Novel 2,3,4,5-tetrahydro-1H-[1,4]diazepino[1,7-a]indole compounds

CLAIMS:

11. The method of claim 8 wherein said disease or disorder is selected from the group consisting of obesity, depression, schizophrenia, a stress related disease, panic disorder, a phobia, obsessive compulsive disorder, post-traumatic-stress syndrome, immune system depression, incontinence, a stress induced problem with the urinary, gastrointestinal or cardiovascular system, neurodegenerative disorders, autism, chemotherapy-induced vomiting, hypertension, migraine headaches, cluster headaches, sexual dysfunction in a mammal, addictive disorder and withdrawal syndrome, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, attention-deficit hyperactivity disorder, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, conduct disorder, cyclothymic disorder, dysthymic disorder, fibromyalgia and other somatoform disorders, generalized anxiety disorder, an inhalation disorder, an intoxication disorder, a movement disorder, oppositional defiant disorder, a pain disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorder, a specific developmental disorder, and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome and combinations thereof.

12. The method of claim 11 wherein said compound is administered rectally, topically, nasally, orally, sublingually, transdermally or parenterally.

DOCUMENT-IDENTIFIER: US 20040147614 A1

TITLE: Method of treating or preventing peripheral neuropathy with a highly selective norepinephrine reuptake inhibitor

CLAIMS:

1. A method of selectively inhibiting reuptake of norepinephrine, the method comprising the step of administering a therapeutically effective amount of a composition to an individual, the composition comprising a compound having a pharmacological selectivity of serotonin (K.sub.i)/norepinephrine (K.sub.i) of at least about 5000.

9. The method of claim 1 wherein said composition is administered orally, topically, parenterally, transdermally, rectally-, or vaginally.

18. The method of claim 1 wherein said condition is selected from the group consisting of at least one of an addictive disorder and withdrawal syndrome, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, attention-deficit hyperactivity disorder, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, chronic or acute stress, chronic pain, conduct disorder, cyclothymic disorder, depression, dysthymic disorder, fibromyalgia and other somatoform disorders, generalized anxiety disorder, incontinence, an inhalation disorder, an intoxication disorder, mania, migraine headaches, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorder, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorder, social phobia, a specific developmental disorder, selective serotonin reuptake inhibition (SSRI) "poop out" syndrome, and TIC disorders.

28. The method of claim 18 wherein incontinence comprises stress incontinence, genuine stress incontinence, or mixed incontinence.

38. A method of treating a human suffering from a condition, or preventing said condition, wherein inhibiting reuptake of norepinephrine provides a benefit, the method comprising the step of administering a therapeutically effective amount of a composition comprising a compound having a pharmacological selectivity of serotonin (K.sub.i)/norepinephrine (K.sub.i) of at least 5000.

39. A method of treating a human suffering from a condition, or preventing said condition, wherein inhibiting reuptake of norepinephrine provides a benefit, while diminishing adverse side effects, the method comprising the step of administering a total dose of about 0.1 to about 10 mg/day of an optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof, to an individual, said optically pure (S,S) reboxetine being substantially free of (R,R) reboxetine.

41. A method of treating or preventing a nervous system disorder comprising the step of administering a therapeutically effective dose of racemic reboxetine or a pharmaceutically acceptable salt thereof to an individual, wherein said disorder is selected from the group consisting of at least one of an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, chronic or acute stress, chronic pain, cyclothymic disorder, dysthymic disorder, fibromyalgia and other somatoform disorders, incontinence, mania, migraine headaches, obesity, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorders, a specific developmental disorders, SSRI "poop out" syndrome, and TIC disorders.

47. The method of claim 41 wherein said reboxetine is administered orally, parenterally, topically, transdermally, rectally, or vaginally.

52. A preparation of a medicament from a composition comprising a compound having a pharmacological selectivity of serotonin (K.sub.i)norepinephrine (K.sub.i) of at least about 5000 to treat or prevent at least one nervous system condition selected from the group consisting of an addictive disorder and withdrawal syndrome, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, attention-deficit hyperactivity disorder, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, chronic or acute stress, chronic pain, conduct disorder, cyclothymic disorder, depression, dysthymic disorder, fibromyalgia and other somatoform disorders, generalized anxiety disorder, incontinence, an inhalation disorder, an intoxication disorder, mania, migraine headaches, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorder, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorder, social phobia, a specific developmental disorder, selective serotonin reuptake inhibition (SSRI) "poop out" syndrome, and TIC disorders.



DOCUMENT-IDENTIFIER: US 20020107249 A1

TITLE: Method of treating or preventing incontinence

CLAIMS:

1. A method of selectively inhibiting reuptake of norepinephrine, the method comprising the step of administering a therapeutically effective amount of a composition to an individual, the composition comprising a compound having a pharmacological selectivity of serotonin (K.sub.i)/norepinephrine (K.sub.i) of at least about 5000.

9. The method of claim 1 wherein said composition is administered orally, topically, parenterally, transdermally, rectally, or vaginally.

18. The method of claim 1 wherein said condition is selected from the group consisting of at least one of an addictive disorder and withdrawal syndrome, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, attention-deficit hyperactivity disorder, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, chronic or acute stress, chronic pain, conduct disorder, cyclothymic disorder, depression, dysthymic disorder, fibromyalgia and other somatoform disorders, generalized anxiety disorder, incontinence, an inhalation disorder, an intoxication disorder, mania, migraine headaches, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorder, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorder, social phobia, a specific developmental disorder, selective serotonin reuptake inhibition (SSRI) "poop out" syndrome, and TIC disorders.

28. The method of claim 18 wherein incontinence comprises stress incontinence, genuine stress incontinence, or mixed incontinence.

38. A method of treating a human suffering from a condition, or preventing said condition, wherein inhibiting reuptake of norepinephrine provides a benefit, the method comprising the step of administering a therapeutically effective amount of a composition comprising a compound having a pharmacological selectivity of serotonin (K.sub.i)/norepinephrine (K.sub.i) of at least about 5000.

39. A method of treating a human suffering from a condition, or preventing said condition, wherein inhibiting reuptake of norepinephrine provides a benefit, while diminishing adverse side effects, the method comprising the step of administering a total dose of about 0.1 to about 10 mg/day of an optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof, to an individual, said optically pure (S,S) reboxetine being substantially free of (R,R) reboxetine.

41. A method of treating or preventing a nervous system disorder comprising the step of administering a therapeutically effective dose of racemic reboxetine or a pharmaceutically acceptable salt thereof to an individual, wherein said disorder is selected from the group consisting of at least one of an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, chronic or acute stress, chronic pain, cyclothymic disorder, dysthymic disorder, fibromyalgia and other somatoform disorders, incontinence, mania, migraine headaches, obesity, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorders, a specific developmental disorders, SSRI "poop out" syndrome, and TIC disorders.

47. The method of claim 41 wherein said reboxetine is administered orally, parenterally, topically, transdermally, rectally, or vaginally.

52. A preparation of a medicament from a composition comprising a compound having a pharmacological selectivity of serotonin (K.sub.i)/norepinephrine (K.sub.i) of at least about 5000 to treat or prevent at least one nervous system condition selected from the group consisting of an addictive disorder and withdrawal syndrome, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, attention-deficit hyperactivity disorder, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, chronic or acute stress, chronic pain, conduct disorder, cyclothymic disorder, depression, dysthymic disorder, fibromyalgia and other somatoform disorders, generalized anxiety disorder, incontinence, an inhalation disorder, an intoxication disorder, mania, migraine headaches, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorder, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorder, social phobia, a specific developmental disorder, selective serotonin reuptake inhibition (SSRI) "poop out" syndrome, and TIC disorders.

DOCUMENT-IDENTIFIER: US 20020061910 A1

TITLE: Method of treating or preventing chronic pain

CLAIMS:

1. A method of selectively inhibiting reuptake of norepinephrine, the method comprising the step of administering a therapeutically effective amount of a composition to an individual, the composition comprising a compound having a pharmacological selectivity of serotonin (K.sub.i)/norepinephrine (K.sub.i) of at least about 5000.

9. The method of claim 1 wherein said composition is administered orally, topically, parenterally, transdermally, rectally, or vaginally.

18. The method of claim 1 wherein said condition is selected from the group consisting of at least one of an addictive disorder and withdrawal syndrome, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, attention-deficit hyperactivity disorder, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, chronic or acute stress, chronic pain, conduct disorder, cyclothymic disorder, depression, dysthymic disorder, fibromyalgia and other somatoform disorders, generalized anxiety disorder, incontinence, an inhalation disorder, an intoxication disorder, mania, migraine headaches, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorder, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorder, social phobia, a specific developmental disorder, selective serotonin reuptake inhibition (SSRI) "poop out" syndrome, and TIC disorders.

28. The method of claim 18 wherein incontinence comprises stress incontinence, genuine stress incontinence, or mixed incontinence.

38. A method of treating a human suffering from a condition, or preventing said condition, wherein inhibiting reuptake of norepinephrine provides a benefit, the method comprising the step of administering a therapeutically effective amount of a composition comprising a compound having a pharmacological selectivity of serotonin (K.sub.i)/norepinephrine (K.sub.i) of at least about 5000.

39. A method of treating a human suffering from a condition or preventing said condition, wherein inhibiting reuptake of norepinephrine provides a benefit, while diminishing adverse side effects, the method comprising the step of administering a total dose of about 0.1 to about 10 mg/day of an optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof, to an individual, said optically pure (S,S) reboxetine being substantially free of (R,R) reboxetine.

41. A method of treating or preventing a nervous system disorder comprising the step of administering a therapeutically effective dose of racemic reboxetine or a pharmaceutically acceptable salt thereof to an individual, wherein said disorder is selected from the group consisting of at least one of an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, chronic or acute stress, chronic pain, cyclothymic disorder, dysthymic disorder, fibromyalgia and other somatoform disorders, incontinence, mania, migraine headaches, obesity, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorders, a specific developmental disorders, SSRI "poop out" syndrome, and TIC disorders.

47. The method of claim 41 wherein said reboxetine is administered orally, parenterally, topically, transdermally, rectally, or vaginally.

52. A preparation of a medicament from a composition comprising a compound having a pharmacological selectivity of serotonin (K.sub.i)/norepinephrine (K.sub.i) of at least about 5000 to treat or prevent at least one nervous system condition selected from the group consisting of an addictive disorder and withdrawal syndrome, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, attention-deficit hyperactivity disorder, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, chronic or acute stress, chronic pain, conduct disorder, cyclothymic disorder, depression, dysthymic disorder, fibromyalgia and other somatoform disorders, generalized anxiety disorder, incontinence, an inhalation disorder, an intoxication disorder, mania, migraine headaches, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorder, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorder, social phobia, a specific developmental disorder, selective serotonin reuptake inhibition (SSRI) "poop out" syndrome, and TIC disorders.

DOCUMENT-IDENTIFIER: US 20020010216 A1

TITLE: New drug combinations

CLAIMS:

1. A composition comprising: (a) a pharmaceutically effective amount of one or more norepinephrine reuptake inhibitors or a pharmaceutically effective salt thereof; and (b) a pharmaceutically effective amount of one or more antimuscarinic agents or a pharmaceutically effective salt thereof.

7. A method for treating incontinence or a disease or disorder of the central nervous system in a mammal comprising administering to said mammal a pharmaceutically effective amount of a composition comprising: (a) a pharmaceutically effective amount of one or more norepinephrine reuptake inhibitors or a pharmaceutically effective salt thereof; and (b) a pharmaceutically effective amount of one or more antimuscarinic agents or a pharmaceutically effective salt thereof.

8. The method according to claim 7 wherein said disease or disorder is selected from the group consisting of obesity, depression, schizophrenia, a stress related disease (e.g. general anxiety disorder), panic disorder, a phobia, obsessive compulsive disorder, post-traumatic-stress syndrome, immune system depression, incontinence, a stress induced problem with the urinary, gastrointestinal or cardiovascular system, neurodegenerative disorders, autism, chemotherapy-induced vomiting, hypertension, migraine headaches, cluster headaches, sexual dysfunction in a mammal, addictive disorder and withdrawal syndrome, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, attention-deficit hyperactivity disorder, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, conduct disorder, cyclothymic disorder, dysthymic disorder, fibromyalgia and other somatoform disorders, generalized anxiety disorder, an inhalation disorder, an intoxication disorder, a movement disorder, oppositional defiant disorder, a pain disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorder, a specific developmental disorder, and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome.

9. The method of claim 7 wherein said composition is administered rectally, topically, orally, sublingually, intranasally, transdermally or parenterally.

12. The method according to claim 7 wherein said disease or disorder comprises incontinence.

13. The method according to claim 12 wherein said incontinence is stress incontinence, genuine stress incontinence or mixed incontinence.

17. The use of a composition comprising: (a) a pharmaceutically effective amount of one or more norepinephrine reuptake inhibitors or a pharmaceutically effective salt thereof; and (b) a pharmaceutically effective amount of one or more antimuscarinic agents or a pharmaceutically effective salt thereof to prepare a medicament for treating or preventing incontinence or diseases or disorders of the central nervous system.

19. A composition comprising: (a) a pharmaceutically effective amount of one or more norepinephrine reuptake inhibitors or a pharmaceutically effective salt thereof; and (b) a pharmaceutically effective amount of one or more antimuscarinic agents or a pharmaceutically effective salt thereof for use as a medicament.

20. A composition comprising: (a) a pharmaceutically effective amount of one or more norepinephrine reuptake inhibitors selected from the group consisting of tandamine, pirandamine, ciclazindol, fluparoxan, lortalamine, talsupram, talopram, prindamine, nomifensine, viloxazine, tomoxetine, duloxetine, venlafaxine, milnacipran and reboxetine and mixtures thereof or a pharmaceutically effective salt thereof; and (b) a pharmaceutically effective amount of one or more antimuscarinic agents selected from the group consisting of tolterodine, propiverine, oxybutynin, trospium, darifenacin, temiverine and ipratropium and mixtures thereof or a pharmaceutically effective salt thereof;

29. A method for treating incontinence or a disease or disorder of the central nervous system in a mammal comprising administering to said mammal a pharmaceutically effective amount of a composition comprising: (a) a pharmaceutically effective amount of one or more norepinephrine reuptake inhibitors tandamine, pirandamine, ciclazindol, fluparoxan, lortalamine, talsupram, talopram, prindamine, nomifensine, viloxazine, tomoxetine, duloxetine, venlafaxine, milnacipran and reboxetine and mixtures thereof or a pharmaceutically effective salt thereof; and (b) a pharmaceutically effective amount of one or more antimuscarinic agents selected from the group consisting of tolterodine, propiverine, oxybutynin, trospium, darifenacin, temiverine and ipratropium and mixtures thereof or a pharmaceutically effective salt thereof.

30. The method according to claim 29 wherein said disease or disorder is selected from the group consisting of obesity, depression, schizophrenia, a stress related disease (e.g. general anxiety disorder), panic disorder, a phobia, obsessive compulsive disorder, post-traumatic-stress syndrome, immune system depression, incontinence, a stress induced problem with the urinary, gastrointestinal or cardiovascular system, neurodegenerative disorders, autism, chemotherapy-induced vomiting, hypertension, migraine headaches, cluster headaches, sexual dysfunction in a mammal, addictive disorder and withdrawal syndrome, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, attention-deficit hyperactivity disorder, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, conduct disorder, cyclothymic disorder, dysthymic disorder, fibromyalgia and other somatoform disorders, generalized anxiety disorder, an inhalation disorder, an intoxication disorder, a movement disorder, oppositional defiant disorder, a pain disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorder, a specific developmental disorder, and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome.

33. The method according to claim 30 wherein said disease or disorder comprises incontinence.

34. The method according to claim 33 wherein said incontinence is stress incontinence, genuine stress incontinence or mixed incontinence.



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(54) **NEW DRUG COMBINATIONS**

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(57) **ABSTRACT**

A composition comprising:

(a) a pharmaceutically effective amount of one or more  
norepinephrine reuptake inhibitors or a pharmaceu-  
tically effective salt thereof; and

(b) a pharmaceutically effective amount of one or more  
neuroleptic agents or a pharmaceutically effective  
salt thereof is provided. The composition is useful in  
treating disorders or diseases of the central nervous  
system, and particularly useful in treating schizo-  
phrenia.

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**2, 2001.**

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TITLE: New drug combinations

CLAIMS:

1. A composition comprising: (a) a pharmaceutically effective amount of one or more norepinephrine reuptake inhibitors or a pharmaceutically effective salt thereof; and (b) a pharmaceutically effective amount of one or more neuroleptic agents or a pharmaceutically effective salt thereof.

9. A method for treating a disease or disorder of the central nervous system in a mammal comprising administering to said mammal a pharmaceutically effective amount of a composition comprising: (a) a pharmaceutically effective amount of one or more selective norepinephrine reuptake inhibitors or a pharmaceutically effective salt thereof; and (b) a pharmaceutically effective amount of one or more neuroleptic agents or a pharmaceutically effective salt thereof.

10. The method according to claim 9 wherein said disease or disorder is selected from the group consisting of obesity, depression, schizophrenia, a stress related disease, panic disorder, a phobia, obsessive compulsive disorder, post-traumatic-stress syndrome, immune system depression, a stress induced problem with the urinary, gastrointestinal or cardiovascular system, neurodegenerative disorders, autism, chemotherapy-induced vomiting, hypertension, migraine headaches, cluster headaches, incontinence, sexual dysfunction, addictive disorder and withdrawal syndrome, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, attention-deficit hyperactivity disorder, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, conduct disorder, cyclothymic disorder, dysthymic disorder, fibromyalgia and other somatoform disorders, generalized anxiety disorder, an inhalation disorder, an intoxication disorder, a movement disorder, oppositional defiant disorder, a pain disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorder, a specific developmental disorder, and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome.

11. The method of claim 9 wherein said composition is administered rectally, topically, orally, sublingually, intranasally, transdermally or parenterally.

19. The use of a composition comprising: (a) a pharmaceutically effective amount of one or more norepinephrine reuptake inhibitors or a pharmaceutically effective salt thereof; and (b) a pharmaceutically effective amount of one or more neuroleptic agents or a pharmaceutically effective salt thereof to prepare a medicament for treating or preventing diseases or disorders of the central nervous system.

22. A composition comprising: (a) a pharmaceutically effective amount of one or more norepinephrine reuptake inhibitors or a pharmaceutically effective salt thereof; and (b) a pharmaceutically effective amount of one or more neuroleptic agents or a pharmaceutically effective salt thereof for use as a medicament.





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(54) **PIPERIDINE-PIPERAZINE LIGANDS FOR  
NEUROTRANSMITTER RECEPTORS**

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(21) Appl. No.: 10/087,609

(22) Filed: Mar. 1, 2002

**Related U.S. Application Data**

(60) Provisional application No. 60/272,966, filed on Mar.  
2, 2001.

**Publication Classification**

(51) Int. Cl.<sup>7</sup> ..... A61K 31/496; C07D 43/02  
(52) U.S. Cl. .... 514/253.13; 544/360

(57) **ABSTRACT**

One aspect of the present invention relates to piperidine-piperazine compounds. A second aspect of the present invention relates to the use of the piperidine-piperazine compounds as ligands for various mammalian cellular receptors or transporters or both, including dopamine, serotonin or norepinephrine receptors or transporters, any combination of them, or all of them. The compounds of the present invention will find use in the treatment of numerous ailments, conditions and diseases which afflict mammals, including but not limited to addiction, anxiety, depression, sexual dysfunction, hypertension, migraine, Alzheimer's disease, obesity, emesis, psychosis, analgesia, schizophrenia, Parkinson's disease, restless leg syndrome, sleeping disorders, attention deficit hyperactivity disorder, irritable bowel syndrome, premature ejaculation, menstrual dysphoria syndrome, urinary incontinence, inflammatory pain, neuropathic pain, Lesche-Nyhan disease, Wilson's disease, and Tourette's syndrome. An additional aspect of the present invention relates to the synthesis of combinatorial libraries of the piperidine-piperazine compounds, and the screening of those libraries for biological activity, e.g., in assays based on dopamine receptors or transporters or both.

DOCUMENT-IDENTIFIER: US 20020123499 A1

TITLE: Piperidine-piperazine ligands for neurotransmitter receptors

CLAIMS:

39. A method of modulating the activity of a dopamine, serotonin, or norepinephrine receptor or transporter in a mammal, comprising the step of: administering to a mammal a therapeutically effective amount of a compound of claim 1.

49. The method of claim 39, wherein said compound is administered topically.

54. A method of modulating the activity of a serotonin receptor or transporter in a mammal, comprising the step of: administering to a mammal a therapeutically effective amount of a compound of claim 1.

64. The method of claim 54, wherein said compound is administered topically.

69. A method of treating a mammal suffering from addiction, anxiety, depression, sexual dysfunction, hypertension, migraine, Alzheimer's disease, obesity, emesis, psychosis, analgesia, schizophrenia, Parkinson's disease, restless leg syndrome, sleeping disorders, attention deficit hyperactivity disorder, irritable bowel syndrome, premature ejaculation, menstrual dysphoria syndrome, urinary incontinence, inflammatory pain, neuropathic pain, Lesche-Nyhan disease, Wilson's disease, or Tourette's syndrome, comprising the step of: administering to a mammal a therapeutically effective amount of a compound of claim 1.

79. The method of claim 69, wherein said compound is administered topically.



US 20020166135A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2002/0166135 A1**

**Waleh et al.**

(43) **Pub. Date: Nov. 7, 2002**

(54) **MODULATORS OF THE HYPOCRETIN SYSTEM AND METHODS OF SCREENING THEREFOR**

(52) **U.S. Cl.** ..... 800/8; 424/85.1; 424/85.5; 424/85.6; 424/85.7

(76) **Inventors:** Nahid S. Waleh, Palo Alto, CA (US);  
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(57) **ABSTRACT**

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Methods for modulating the hypocretin system, as well as methods for identifying compounds that act as hypocretin-system modulators are provided. In modulating the hypocretin system, the method comprises administering a therapeutically effective amount of a preprohypocretin-expression modulator to an individual, wherein the preprohypocretin-expression modulator alters preprohypocretin expression in preprohypocretin-expressing cells. The method for identifying compounds comprises contacting a test compound to cells equipped with the 5' flanking promoter of the preprohypocretin gene operably linked to a nucleic acid sequence and determining whether the test compound alters transcription of the nucleic acid sequence in the cell, wherein the test compound's ability to alter transcription is indicative of a compound that modulates the hypocretin system. The invention also provides compounds; pharmaceutical compositions, nucleic acid sequences, expression vectors, transformed host cells, and the like for carrying out the methods.

(21) **Appl. No.:** 10/029,427

(22) **Filed:** Dec. 19, 2001

**Related U.S. Application Data**

(60) **Provisional application No. 60/258,069, filed on Dec. 20, 2000.**

**Publication Classification**

(51) **Int. Cl.<sup>7</sup>** ..... A01K 67/00; A61K 38/21

PGPUB-DOCUMENT-NUMBER: 20020166135  
PGPUB-FILING-TYPE: new  
DOCUMENT-IDENTIFIER: US 20020166135 A1

TITLE: Modulators of the hypocretin system and methods of screening therefor

PUBLICATION-DATE: November 7, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
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Kilduff, Thomas S.	Menlo Park	CA	US

US-CL-CURRENT: 800/8; 424/85.1, 424/85.5, 424/85.6, 424/85.7

CLAIMS:

What is claimed is:

1. A method for modulating the hypocretin system in an individual comprising administering a therapeutically effective amount of a preprohypocretin-expression modulator to the individual, wherein the preprohypocretin-expression modulator alters preprohypocretin expression in preprohypocretin-expressing cells.
2. The method of claim 1, wherein the modulator enhances preprohypocretin expression.
3. The method of claim 2, wherein the modulator binds to the 5' flanking promoter of the preprohypocretin gene.
4. The method of claim 1, wherein the modulator decreases preprohypocretin expression.
5. The method of claim 4, wherein the modulator binds to the 5'-flanking promoter of the preprohypocretin gene.
6. The method of claim 5, wherein the modulator is a cytokine.
7. The method of claim 6, wherein the cytokine is an interferon.
8. The method of claim 7, wherein the interferon is selected from the group consisting of alpha-interferon, beta-interferon, gamma-interferon, and combinations thereof.
9. The method of claim 8, wherein the interferon is alpha-interferon.
10. The method of claim 1, wherein modulation of the hypocretin system in the individual results in a change in the individual's sleep pattern.
11. The method of claim 10, wherein the individual suffers from a sleep disorder.
12. The method of claim 11, wherein the sleep disorder is an age-related sleep disorder.

13. The method of claim 11, wherein the sleep disorder is due to jet-lag.
14. The method of claim 10, wherein the modulator enhances preprohypocretin expression, thereby decreasing the individual's desire for sleep.
15. The method of claim 14, wherein the individual suffers from narcolepsy.
16. The method of claim 10, wherein the modulator decreases preprohypocretin expression, thereby increasing the individual's desire for sleep.
17. The method of claim 16, wherein the individual suffers from insomnia.
18. The method of claim 1, wherein the individual suffers from a mood disorder, chronic fatigue syndrome, or an attention deficit disorder.
19. The method of claim 1, wherein the individual suffers from neuronal degeneration resulting from prior ischemic events, and modulation of the hypocretin system alleviates said neuronal degeneration.
20. The method of claim 1, wherein the individual suffers from nausea or vomiting, and modulation of the hypocretin system alleviates said nausea or vomiting.
21. The method of claim 1, wherein the individual suffers from irritable bowel syndrome, and modulation of the hypocretin system alleviates said irritable bowel syndrome.
22. The method of claim 1, wherein the individual suffers from incontinence, and modulation of the hypocretin system alleviates said incontinence.
23. The method of claim 1, wherein the individual suffers from visceral pain, and modulation of the hypocretin system alleviates said visceral pain.
24. The method of claim 1, wherein the individual suffers from an eating disorder, and modulation of the hypocretin system alleviates said eating disorders.
25. The method of claim 1, wherein the individual is a human.
26. The method of claim 1, wherein the preprohypocretin-expressing cell is located in the posterior lateral hypothalamus.
27. The method of claim 1, wherein the preprohypocretin-expressing cell is located in a peripheral tissue.
28. The method of claim 27, wherein the peripheral tissue is bladder tissue.
29. The method of claim 27, wherein the peripheral tissue is tissue comprising the gastrointestinal tract.
30. The method of claim 1, wherein the modulator is administered orally, parenterally, rectally, buccally, sublingually, nasally, by inhalation, topically, transdermally, intracerebralventricularly or via an implanted reservoir.
31. The method of claim 1, wherein the modulator is administered together with a pharmaceutically

acceptable carrier as a pharmaceutical composition.

32. The method of claim 1, further comprising administration of one or more additional active agents.

33. The method of claim 32, wherein the additional active agent is selected from the group consisting of wakefulness-promoting drugs, tricyclic antidepressants, tetracyclic antidepressants, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, and combinations thereof.

34. The method of claim 32, wherein the additional active agent is selected from the group consisting of modafinil, amphetamine, amphetamine homologues, caffeine, cocaine, cathinone, ephedrine, theophylline, theobromine, methylphenidate, dextroamphetamine, methamphetamine, pemoline, phenmetrazine, mazindol, selegiline, ritanserin, violoxazine, CRL40476, clomipramine, imipramine, desipramine, fluoxetine, paroxetine, sertraline, gammahydroxybutyrate, clonazepam, carbamazepine, yohimbine, and combinations thereof.

35. The method of claim 14, further comprising administration of one or more additional active agents.

36. A method of treating a narcoleptic patient comprising administering a therapeutically effective amount of a preprohypocretin-expression modulator to the individual, wherein the preprohypocretin-expression modulator enhances preprohypocretin expression in preprohypocretin-expressing cells located in the posterior lateral hypothalamus.

37. The method of claim 36, wherein the preprohypocretin-expression modulator binds to the 5' flanking promoter of the preprohypocretin gene.

38. The method of claim 37, wherein the preprohypocretin-expression modulator is a cytokine.

39. The method of claim 36, wherein the individual is a human.

40. The method of claim 36, further comprising administration of an additional active agent.

41. The method of claim 40, wherein the additional active agent is selected from the group consisting of amphetamine, amphetamine homologues, caffeine, cathinone, cocaine, ephedrine, methamphetamine, methylphenidate, modafinil, pemoline, phenmetrazine, and combinations thereof.

42. The method of claim 36, wherein the modulator is administered orally, parenterally, rectally, buccally, sublingually, nasally, by inhalation, topically, transdermally, intracerebralventricularly or via an implanted reservoir.

43. The method of claim 36, wherein the modulator is administered together with a pharmaceutically acceptable carrier as a pharmaceutical composition.

44. A method for identifying a compound that modulates the hypocretin system comprising contacting a test compound to cells equipped with the 5' flanking promoter of the preprohypocretin gene operably linked to a nucleic acid sequence and determining whether the test compound alters transcription of the nucleic acid sequence in the cells, wherein the test compound's ability to alter transcription is indicative of a compound that modulates the hypocretin system.

45. The method of claim 44, wherein the cells are a naturally occurring preprohypocretin-expressing cells.

46. The method of claim 44, wherein the cells are genetically manipulated to be equipped with the 5' flanking promoter of the preprohypocretin gene.
47. The method of claim 46, wherein the nucleic acid sequence codes for a known gene.
48. The method of claim 47, wherein alteration of transcription is evidenced by a change in expression of the gene when compared to expression of the gene without the compound.
49. The method of claim 48, wherein the compound enhances expression of the gene.
50. The method of claim 49, wherein the compound binds to the 5'-flanking promoter of the preprohypocretin gene.
51. The method of claim 48, wherein the compound decreases expression of the gene.
52. The method of claim 51, wherein the compound binds to the 5'-flanking promoter of the preprohypocretin gene.
53. The method of claim 44, which is carried out in vitro.
54. An isolated DNA fragment coding for the 5' flanking promoter of the preprohypocretin gene.
55. The isolated DNA fragment of claim 54, comprising the nucleotide sequence of SEQ ID NO: 1.
56. An expression vector comprising the DNA fragment of claim 54.
57. The expression vector of claim 56, wherein the DNA fragment comprises the nucleotide sequence of SEQ ID NO: 1.
58. A host cell transformed with the expression vector of claim 56.
59. A compound that modulates the hypocretin system, wherein the compound is identified by the steps comprising contacting a preprohypocretin-expressing cell with the compound and determining whether the compound alters preprohypocretin expression in the preprohypocretin-expressing cell, wherein the compound's ability to alter preprohypocretin expression is indicative of a compound that modulates the hypocretin system.
60. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 59.
61. The composition of claim 60, further comprising a pharmaceutically acceptable carrier.

DOCUMENT-IDENTIFIER: US 20020169317 A1

TITLE: Oxazinocarbazoles for the treatment of CNS diseases

## CLAIMS:

29. The method of claim 24 wherein the disease is obesity, depression, schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, a stress related disease (e.g. general anxiety disorder), panic disorder, a phobia, obsessive compulsive disorder, post-traumatic-stress syndrome, immune system depression, a stress induced problem with the urinary, gastrointestinal or cardiovascular system (e.g., stress incontinence), neurodegenerative disorders, autism, chemotherapy-induced vomiting, hypertension, migraine headaches, cluster headaches, sexual dysfunction in a mammal (e.g. a human), addictive disorder and withdrawal syndrome, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, attention-deficit hyperactivity disorder, behavioral disturbance (including agitation in conditions associated with diminished cognition (e.g., dementia, mental retardation or delirium)), bipolar disorder, bulimia nervosa, chronic fatigue syndrome, conduct disorder, cyclothymic disorder, dysthymic disorder, fibromyalgia and other somatoform disorders, generalized anxiety disorder, an inhalation disorder, an intoxication disorder, movement disorder (e.g., Huntington's disease or Tardive Dyskinesia), oppositional defiant disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder (brief and long duration disorders, psychotic disorder due to medical condition, psychotic disorder NOS), mood disorder (major depressive or bipolar disorder with psychotic features) seasonal affective disorder, a sleep disorder, a specific developmental disorder, agitation disorder, selective serotonin reuptake inhibition (SSRI) "poop out" syndrome or Tourette's syndrome.

31. The method of claim 14 wherein said compound is administered rectally, topically, nasally, orally, sublingually, transdermally or parenterally.



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L14: Entry 4 of 25

File: PGPB

Dec 23, 2004

DOCUMENT-IDENTIFIER: US 20040260272 A1

TITLE: Method and system for intravesicular delivery of therapeutic agentsDetail Description Paragraph:

[0270] Some literature of interest in connection with delivery of agents via the bladder includes: Fraser et al., "The Future of Bladder Control-Intravesical Drug Delivery, a Pinch of Pepper, and Gene Therapy" Reviews in Urology vol. 4, no. 1 (2002); Szallasi, A., et al., AResiniferatoxin-type phorboid vanilloids display capsaicin-like selectivity at native vanilloid receptors on rat DRG neurons and at the cloned vanilloid receptor VR1., 1999., 128(2):, 428-434.; Macha, A., et al.; "Aphorboid 20-homovanillates induce apoptosis through a VR1-independent mechanism.", Chem. Biol., 2000, 7(7):, 483-492. Szallasi, A., & P. M. Blumberg. and AVanilloid (Capsaicin) receptors and mechanisms, Pharmacol. Rev., 1999, 51:, 159.

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L14: Entry 9 of 25

File: PGPB

Jul 15, 2004

DOCUMENT-IDENTIFIER: US 20040138252 A1

TITLE: Pharmaceutical composition for therapy of interstitial cystitis

Summary of Invention Paragraph:

[0005] With respect to drugs to treat interstitial cystitis, the intravesical administration of dimethyl sulfoxide (DMSO) is approved by Food and Drug Administration in the United States, and its mechanism of action is considered to be desensitization of capsaicin-sensitive sensory nerves (Expert Opinion on Invest Drug, 10: p.521 and J. Urol., 158: pp.1989-1995). Also, it is reported that the intravesical instillation of capsaicin or resiniferatoxin, that is with the same pharmacological action, improves pain or other symptoms of interstitial cystitis in clinical testing (J. Urol., 157, Suppl: p.254 (1997) and J. Urol., 163, Suppl: p.60 (2000)).

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L14: Entry 3 of 25

File: PGPB

Jul 7, 2005

DOCUMENT-IDENTIFIER: US 20050148587 A1

TITLE: Thiazolidinone, oxazolidinone, and imidazolone derivatives for treating lower urinary tract and related disorders

Brief Description of Drawings Paragraph:

[0013] FIG. 1. FIG. 1 depicts intermicturition intervals before (Sal) and after (remaining groups) bladder hyperactivity caused by continuous intravesical dilute acetic acid infusion. .omega.-Conotoxin MVIIA was administered intrathecally at increasing doses, and data is represented as Mean ( $\pm$  SEM) intermicturition intervals in minutes.

Brief Description of Drawings Paragraph:

[0014] FIG. 2. FIG. 2 depicts bladder capacity before (Sal) and after (remaining groups) bladder hyperactivity caused by continuous intravesical dilute acetic acid infusion. .omega.-Conotoxin MVIIA was administered intrathecally at increasing doses and data has been normalized to irritation control values (AA/Veh3) and is represented as Mean ( $\pm$  SEM).

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DOCUMENT-IDENTIFIER: US 6630515 B2

TITLE: Urinary incontinence therapy

Other Reference Publication (1):

Craft, R.M. and Porreca, F. "Temporal Parameters of Desensitization to Intravesical Resiniferatoxin in the Rat"; Physiology & Behavior (1994) 56(3):479-485.

Other Reference Publication (2):

Craft, R.M. and Porreca, F. "Tetracaine attenuates irritancy without attenuating desensitization produced by intravesical resiniferatoxin in the rat"; Pain (1994) 57:351-359.

Other Reference Publication (3):

Craft, R.M. et al. "Long-lasting desensitization of bladder afferents following intravesical resiniferatoxin and capsaicin in the rat"; Pain 61:317-323, 1993.

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US006825185B2

(12) **United States Patent**  
Khanapure et al.

(10) Patent No.: **US 6,825,185 B2**  
(45) Date of Patent: **Nov. 30, 2004**

(54) **SUBSTITUTED ARYL COMPOUNDS AS NOVEL CYCLOOXYGENASE-2 SELECTIVE INHIBITORS, COMPOSITIONS AND METHODS OF USE**

(75) Inventors: Subhash P. Khanapure, Clinton, MA (US); David S. Garvey, Dover, MA (US); Richard A. Earl, Westford, MA (US); Malko Ezawa, Acton, MA (US); Xinqin Fang, Lexington, MA (US); Ricky D. Gaston, Malden, MA (US)

(73) Assignee: NitroMed, Inc., Lexington, MA (US)

(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: 10/730,979

(22) Filed: Dec. 10, 2003

(65) Prior Publication Data

US 2004/0116431 A1 Jun. 17, 2004

#### Related U.S. Application Data

(62) Division of application No. 10/024,046, filed on Dec. 21, 2001, now Pat. No. 6,706,724.

(60) Provisional application No. 60/256,932, filed on Dec. 21, 2000.

(51) Int. Cl.<sup>7</sup> ..... A61K 31/33; A61K 31/505; A61K 31/435; C07D 237/00; C07D 239/00

(52) U.S. Cl. .... 514/183; 514/277; 514/252.05; 514/256; 514/365; 514/367; 514/374; 514/375; 514/461; 514/469; 544/224; 544/242; 546/1

(58) Field of Search ..... 514/183, 277, 514/252.01, 256, 365, 367, 374, 375, 461, 469; 546/1; 544/224, 242

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Oct. 27, 2003. International Search Report from International Application No. PCT/US01/48823.

Primary Examiner—Richard L. Raymond

Assistant Examiner—Sudhaker B. Patel

(74) Attorney, Agent, or Firm—Wilmer Cutler Pickering Hale and Dorr LLP

(57) **ABSTRACT**

The invention describes novel substituted aryl compounds that are cyclooxygenase 2 (COX-2) selective inhibitors and novel compositions comprising at least one cyclooxygenase 2 (COX-2) selective inhibitor, and, optionally, at least one compound that donates, transfers or releases nitric oxide, stimulates endogenous synthesis of nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor or is a substrate for nitric oxide synthase, and/or, optionally, at least one therapeutic agent, such as, steroids, nonsteroidal antiinflammatory compounds (NSAID), 5-lipoxygenase (5-LO) inhibitors, leukotriene B<sub>4</sub> (LTB<sub>4</sub>) receptor antagonists, leukotriene A<sub>4</sub> (LTA<sub>4</sub>) hydrolase inhibitors, 5-HT agonists, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) inhibitors, H<sub>2</sub> antagonists, antineoplastic agents, antiplatelet agents, thrombin inhibitors, thromboxane inhibitors, decongestants, diuretics, sedating or non-sedating anti-histamines, inducible nitric oxide synthase inhibitors, opioids, analgesics, *Helicobacter pylori* inhibitors, proton pump inhibitors, isoprostane inhibitors, and mixtures thereof. The invention also provides novel kits comprising at least one COX-2 selective inhibitor, and, optionally, at least one nitric oxide donor, and/or, optionally, at least one therapeutic agent. The novel cyclooxygenase 2 selective inhibitors of the invention can be optionally nitrosated and/or nitrosylated. The invention also provides methods for treating inflammation, pain and fever; for treating and/or improving the gastrointestinal properties of COX-2 selective inhibitors; for facilitating wound healing; for treating and/or preventing renal toxicity or other toxicities; for treating and/or preventing other disorders resulting from elevated levels of cyclooxygenase-2; and for improving the cardiovascular profile of COX-2 selective inhibitors.

54 Claims, No Drawings

DOCUMENT-IDENTIFIER: US 6825185 B2

TITLE: Substituted aryl compounds as novel cyclooxygenase-2 selective inhibitors, compositions and methods of use

CLAIMS:

7. The method of claim 6, wherein the disorder resulting from elevated levels of COX-2 is angiogenesis, arthritis, asthma, bronchitis, menstrual cramps, premature labor, tendonitis, bursitis, a skin-related condition, neoplasia, inflammation in disease, ophthalmic disorder, pulmonary inflammation, central nervous system disorder, allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis, inflammation, microbial infection, cardiovascular disorder, urinary disorder, urological disorder, endothelial dysfunction, a disorder treated by the preservation of organs and tissues, a disorder treated by inhibition of activation, adhesion and infiltration of neutrophils at the site of inflammation, or a disorder treated by inhibition of platelet aggregation.

17. The method of claim 16, wherein the compound of claim 2 or a pharmaceutically acceptable salt thereof, and the least one of a 3-hydroxy-3-methylglutaryl coenzyme A, an antiplatelet agent, a thrombin inhibitor or a thromboxane inhibitor are administered orally, buccally, topically, by injection, by inhalation, or by transdermal application.

28. The composition of claim 18, wherein the therapeutic agent is a steroid, a nonsteroidal antiinflammatory compound, a 5-lipoxygenase inhibitor, a leukotriene B.sub.4 receptor antagonist, a leukotriene A.sub.4 hydrolase inhibitor, a 5-HT agonist, a 3-hydroxy-3-methylglutaryl coenzyme A inhibitor, a H.sub.2 receptor antagonist, an antineoplastic agent, an antiplatelet agent, a thrombin inhibitor, a thromboxane inhibitor, a decongestant, a diuretic, a sedating or non-sedating anti-histamine, an inducible nitric oxide synthase inhibitor, an opioid, an analgesic, a Helicobacter pylori inhibitor, a proton pump inhibitor, an isoprostane inhibitor, or a mixture of two or more thereof.

30. The composition of claim 29, wherein the therapeutic agent is a steroid, a nonsteroidal antiinflammatory compound, a 5-lipoxygenase inhibitor, a leukotriene B.sub.4 receptor antagonist, a leukotriene A.sub.4 hydrolase inhibitor, a 5-HT agonist, a 3-hydroxy-3-methylglutaryl coenzyme A inhibitor, a H.sub.2 receptor antagonist, an antineoplastic agent, an antiplatelet agent, a thrombin inhibitor, a thromboxane inhibitor, a decongestant, a diuretic, a sedating or non-sedating anti-histamine, an inducible nitric oxide synthase inhibitor, an opioid, an analgesic, a Helicobacter pylori inhibitor, a proton pump inhibitor, an isoprostane inhibitor, or a mixture of two or more thereof.

33. The method of claim 32, wherein the disorder resulting from elevated levels of COX-2 is angiogenesis, arthritis, asthma, bronchitis, menstrual cramps, premature labor, tendonitis, bursitis, a skin-related condition, neoplasia, inflammation in disease, ophthalmic disorder, pulmonary inflammation, central nervous system disorder, allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis, inflammation, microbial infection, cardiovascular disorder, urinary disorder, urological disorder, endothelial dysfunction, a disorder treated by the preservation of organs and tissues, a disorder treated by inhibition of activation, adhesion and infiltration of neutrophils at the site of inflammation, or a disorder treated by inhibition of platelet aggregation.

42. The composition of claim 18, wherein the least one compound of claim 1 or a pharmaceutically acceptable salt thereof, the least one compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase and the at least one therapeutic agents are administered orally, buccally, topically, by injection, by inhalation, or by transdermal application.

DOCUMENT-IDENTIFIER: US 20020119977 A1

TITLE: Substituted aryl compounds as novel cyclooxygenase-2 selective inhibitors, compositions and methods of use related applications

CLAIMS:

7. The method of claim 6, wherein the disorder resulting from elevated levels of COX-2 is angiogenesis, arthritis, asthma, bronchitis, menstrual cramps, premature labor, tendinitis, bursitis, a skin-related condition, neoplasia, inflammation in disease, ophthalmic disorder, pulmonary inflammation, central nervous system disorder, allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis, inflammation and/or microbial infection, cardiovascular disorder, urinary and/or urological disorder, endothelial dysfunction, a disorder treated by the preservation of organs and tissues, a disorder treated by inhibition and/or prevention of activation, adhesion and infiltration of neutrophils at the site of inflammation, or a disorder treated by inhibition and/or prevention of platelet aggregation.

17. The method of claim 16, wherein the compound of Formula (I) or a pharmaceutically acceptable salt thereof, and the least one of a 3-hydroxy-3-methylglutaryl coenzyme A, an antiplatelet agent, a thrombin inhibitor or a thromboxane inhibitor are administered orally, buccally, topically, by injection, by inhalation, or by transdermal application.

28. The composition of claim 18, wherein the therapeutic agent is a steroid, a nonsteroidal antiinflammatory compound, a 5-lipoxygenase inhibitor, a leukotriene B.sub.4 receptor antagonist, a leukotriene A.sub.4 hydrolase inhibitor, a 5-HT agonist, a 3-hydroxy-3-methylglutaryl coenzyme A inhibitor, a H.sub.2 receptor antagonist, an antineoplastic agent, an antiplatelet agent, a thrombin inhibitor, a thromboxane inhibitor, a decongestant, a diuretic, a sedating or non-sedating anti-histamine, an inducible nitric oxide synthase inhibitor, an opioid, an analgesic, a Helicobacter pylori inhibitor, a proton pump inhibitor, an isoprostane inhibitor, or a mixture thereof.

30. The composition of claim 29, wherein the therapeutic agent is a steroid, a nonsteroidal antiinflammatory compound, a 5-lipoxygenase inhibitor, a leukotriene B.sub.4 receptor antagonist, a leukotriene A.sub.4 hydrolase inhibitor, a 5-HT agonist, a 3-hydroxy-3-methylglutaryl coenzyme A inhibitor, a H.sub.2 receptor antagonist, an antineoplastic agent, an antiplatelet agent, a thrombin inhibitor, a thromboxane inhibitor, a decongestant, a diuretic, a sedating or non-sedating anti-histamine, an inducible nitric oxide synthase inhibitor, an opioid, an analgesic, a Helicobacter pylori inhibitor, a proton pump inhibitor, an isoprostane inhibitor, or a mixture thereof.

33. The method of claim 32, wherein the disorder resulting from elevated levels of COX-2 is angiogenesis, arthritis, asthma, bronchitis, menstrual cramps, premature labor, tendinitis, bursitis, skin-related condition, neoplasia, inflammation in disease, ophthalmic disorder, pulmonary inflammation, central nervous system disorder, allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis, inflammation and/or microbial infection, cardiovascular disorder, urinary and/or urological disorder, endothelial dysfunction, a disorder treated by the preservation of organs and tissues, a disorder treated by inhibition and/or prevention of activation, adhesion and infiltration of neutrophils at the site of inflammation, or a disorder treated by inhibition and/or prevention of platelet aggregation.

42. The composition of claim 18, wherein the least one compound of Formula (I) or a pharmaceutically acceptable salt thereof, the least one compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for

nitric oxide synthase and the at least one therapeutic agents are administered orally, buccally, topically, by injection, by inhalation, or by transdermal application.





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(19) **United States**(12) **Patent Application Publication**  
Khanapure et al.(10) Pub. No.: **US 2004/0116431 A1**(43) Pub. Date: **Jun. 17, 2004**(54) **SUBSTITUTED ARYL COMPOUNDS AS  
NOVEL CYCLOOXYGENASE-2 SELECTIVE  
INHIBITORS, COMPOSITIONS AND  
METHODS OF USE**

544/182; 544/238; 544/333

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(57) **ABSTRACT**

The invention describes novel substituted aryl compounds that are cyclooxygenase 2 (COX-2) selective inhibitors and novel compositions comprising at least one cyclooxygenase 2 (COX-2) selective inhibitor, and, optionally, at least one compound that donates, transfers or releases nitric oxide, stimulates endogenous synthesis of nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor or is a substrate for nitric oxide synthase, and/or, optionally, at least one therapeutic agent, such as, steroids, nonsteroidal antiinflammatory compounds (NSAID), 5-lipoxygenase (5-LO) inhibitors, leukotriene B<sub>4</sub> (LTB<sub>4</sub>) receptor antagonists, leukotriene A<sub>4</sub> (LTA<sub>4</sub>) hydrolase inhibitors, 5-HT agonists, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) inhibitors, H<sub>2</sub> antagonists, antineoplastic agents, anti-platelet agents, thrombin inhibitors, thromboxane inhibitors, decongestants, diuretics, sedating or non-sedating anti-histamines, inducible nitric oxide synthase inhibitors, opioids, analgesics, *Helicobacter pylori* inhibitors, proton pump inhibitors, isoprostane inhibitors, and mixtures thereof. The invention also provides novel kits comprising at least one COX-2 selective inhibitor, and, optionally, at least one nitric oxide donor, and/or, optionally, at least one therapeutic agent. The novel cyclooxygenase 2 selective inhibitors of the invention can be optionally nitrosated and/or nitrosylated. The invention also provides methods for treating inflammation, pain and fever; for treating and/or improving the gastrointestinal properties of COX-2 selective inhibitors; for facilitating wound healing; for treating and/or preventing renal toxicity or other toxicities; for treating and/or preventing other disorders resulting from elevated levels of cyclooxygenase-2; and for improving the cardiovascular profile of COX-2 selective inhibitors.

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TITLE: Substituted aryl compounds as novel cyclooxygenase-2 selective inhibitors, compositions and methods of use

CLAIMS:

7. The method of claim 6, wherein the disorder resulting from elevated levels of COX-2 is angiogenesis, arthritis, asthma, bronchitis, menstrual cramps, premature labor, tendonitis, bursitis, a skin-related condition, neoplasia, inflammation in disease, ophthalmic disorder, pulmonary inflammation, central nervous system disorder, allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis, inflammation, microbial infection, cardiovascular disorder, urinary disorder, urological disorder, endothelial dysfunction, a disorder treated by the preservation of organs and tissues, a disorder treated by inhibition of activation, adhesion and infiltration of neutrophils at the site of inflammation, or a disorder treated by inhibition of platelet aggregation.

17. The method of claim 16, wherein the compound of claim 2 or a pharmaceutically acceptable salt thereof, and the least one of a 3-hydroxy-3-methylglutaryl coenzyme A, an antiplatelet agent, a thrombin inhibitor or a thromboxane inhibitor are administered orally, buccally, topically, by injection, by inhalation, or by transdermal application.

28. The composition of claim 18, wherein the therapeutic agent is a steroid, a nonsteroidal antiinflammatory compound, a 5-lipoxygenase inhibitor, a leukotriene B.sub.4 receptor antagonist, a leukotriene A.sub.4 hydrolase inhibitor, a 5-HT agonist, a 3-hydroxy-3-methylglutaryl coenzyme A inhibitor, a H.sub.2 receptor antagonist, an antineoplastic agent, an antiplatelet agent, a thrombin inhibitor, a thromboxane inhibitor, a decongestant, a diuretic, a sedating or non-sedating anti-histamine, an inducible nitric oxide synthase inhibitor, an opioid, an analgesic, a Helicobacter pylori inhibitor, a proton pump inhibitor, an isoprostane inhibitor, or a mixture of two or more thereof.

30. The composition of claim 29, wherein the therapeutic agent is a steroid, a nonsteroidal antiinflammatory compound, a 5-lipoxygenase inhibitor, a leukotriene B.sub.4 receptor antagonist, a leukotriene A.sub.4 hydrolase inhibitor, a 5-HT agonist, a 3-hydroxy-3-methylglutaryl coenzyme A inhibitor, a H.sub.2 receptor antagonist, an antineoplastic agent, an antiplatelet agent, a thrombin inhibitor, a thromboxane inhibitor, a decongestant, a diuretic, a sedating or non-sedating anti-histamine, an inducible nitric oxide synthase inhibitor, an opioid, an analgesic, a Helicobacter pylori inhibitor, a proton pump inhibitor, an isoprostane inhibitor, or a mixture of two or more thereof.

33. The method of claim 32, wherein the disorder resulting from elevated levels of COX-2 is angiogenesis, arthritis, asthma, bronchitis, menstrual cramps, premature labor, tendonitis, bursitis, a skin-related condition, neoplasia, inflammation in disease, ophthalmic disorder, pulmonary inflammation, central nervous system disorder, allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis, inflammation, microbial infection, cardiovascular disorder, urinary disorder, urological disorder, endothelial dysfunction, a disorder treated by the preservation of organs and tissues, a disorder treated by inhibition of activation, adhesion and infiltration of neutrophils at the site of inflammation, or a disorder treated by inhibition of platelet aggregation.

42. The composition of claim 18, wherein the least one compound of claim 1 or a pharmaceutically acceptable salt thereof, the least one compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase and the at least one therapeutic agents are administered orally, buccally, topically, by injection, by inhalation, or by transdermal application.

## BOTULINUM-A TOXIN FOR TREATING DETRUSOR HYPERREFLEXIA IN SPINAL CORD INJURED PATIENTS: A NEW ALTERNATIVE TO ANTICHOLINERGIC DRUGS? PRELIMINARY RESULTS

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### ABSTRACT

**Purpose:** We evaluated the efficacy of botulinum-A toxin injections into the detrusor muscle in patients with spinal cord injury, detrusor hyperreflexia and urge incontinence resistant to anticholinergic drugs. The purpose of treatment was to suppress incontinence episodes and increase functional bladder capacity.

**Materials and Methods:** Included in our prospective nonrandomized study done at 2 clinics were 31 patients with traumatic spinal cord injury who emptied the bladder by intermittent self-catheterization. These patients had severe detrusor hyperreflexia and incontinence despite a high dose of anticholinergic medication. Pretreatment evaluation included a clinical examination and complete urodynamic investigation. Under cystoscopic control a total of 200 to 300 units of botulinum-A toxin were injected into the detrusor muscle at 20 to 30 sites (10 units per ml. per site), sparing the trigone. Clinical and urodynamic followup was planned for 6, 16 and 36 weeks after treatment. Patients were asked to decrease their intake of anticholinergic drugs during week 1 after treatment.

**Results:** Of the 21 patients 19 underwent a complete examination 6 weeks after the botulinum-A toxin injections, and 11 at 16 and 36 weeks. At the 6-week followup complete continence was restored in 17 of 19 cases in which anticholinergic medication was markedly decreased or withdrawn. Less satisfactory results in 2 cases were associated with an insufficient dose of 200 units botulinum-A toxin. After the injections overall mean reflex volume and mean maximum cystometric bladder capacity plus or minus standard deviation significantly increased from  $215.8 \pm 90.4$  ml. to  $415.7 \pm 211.1$  (p < 0.016) and  $296.3 \pm 145.2$  to  $480.5 \pm 134.1$  (p < 0.016), respectively. There was also a significant decrease after treatment in mean maximum detrusor voiding pressure from  $65.6 \pm 29.2$  cm. water to  $35 \pm 32.1$  (p < 0.016). Mean post-void residual urine volume catheterized at the end of the urodynamic examination increased significantly from a mean of  $261.8 \pm 241.3$  ml. to  $490.5 \pm 204.8$  (p < 0.016). Moreover, autonomic dysreflexia associated with bladder emptying that manifested as a hypertensive crisis during voiding disappeared after treatment in the 3 patients with tetraplegia. Satisfaction was high in all successfully treated patients and no side effects were observed. Ongoing improvement in urodynamic parameters and incontinence was already present in all patients reevaluated at 16 and 36 weeks.

**Conclusions:** Botulinum-A toxin injections into the detrusor seem to be a safe and valuable therapeutic option in spinal cord injured patients with incontinence resistant to anticholinergic medication who perform clean intermittent self-catheterization. Successfully treated patients become continent again and may withdraw from or markedly decrease anticholinergic drug intake. A dose of 300 units botulinum-A toxin seems to be needed to counteract an overactive detrusor. The duration of bladder paresis induced by the toxin is at least 9 months, when repeat injections are required.

**KEY WORDS:** bladder; bladder, neurogenic; spinal cord injuries; botulinum toxin type A; urinary incontinence

Incontinence of neurological origin is most often due to detrusor hyperreflexia. Current treatment relies on anticholinergic medication to block partially the efferent parasympathetic innervation to the detrusor.<sup>1</sup> However, these drugs have troublesome side effects and may be insufficiently effective to restore continence in patients with severe hyperreflexia. Although other treatments are available to block the afferent arc of the reflex that causes detrusor contractions, sacral root rhizotomy is best restricted to patients with a complete suprasa-

cral cord lesion and is of limited usefulness in men who otherwise want to preserve reflex erections.<sup>2</sup> Injecting phenol into the subtrigonal region of the bladder provides only a transient benefit and has various complications, making this procedure unsuitable for repeat administration.<sup>3</sup> Capsaicin interferes with sensory unmyelinated C and thinly myelinated A-δ fibers and, thus, it was considered effective for treating detrusor hyperreflexia in patients with multiple sclerosis or spinal cord injury.<sup>4,5</sup> However, there are controversial results in the literature and some patients appear not to respond to this treatment.<sup>6-9</sup> The new phenol related diterpene analogue resiniferatoxin is 100 to 10,000-fold more potent than capsaicin for causing functional desensitization of the sensory fibers without previous neuron excitation, and may represent an alternative to

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capsaicin.<sup>10-12</sup> However, to our knowledge only preliminary data on phases 1 and 2 are currently available. Phase 3 studies are still required to judge the efficiency of this new therapeutic approach.<sup>13</sup> Short-term maximum functional stimulation of the pudendal nerve afferents or implantation of a sacral root pudendal for nerve stimulator may result in major benefits for urge incontinence.<sup>14,15</sup> However, a long-term effect is seldom expected when there is a neurogenic lesion.<sup>16</sup>

To date little nonsurgical help has been offered to patients with severe neurogenic incontinence. Botulinum-A toxin selectively blocks the release of acetylcholine from nerve endings. Reports are increasing of its efficacy in conditions caused by focal smooth muscle contraction, such as achalasia, or parasympathetic autonomic disorders, such as hyperhidrosis and gustatory sweating.<sup>17-20</sup> Our hypothesis was that injections of botulinum-A toxin into the detrusor muscle would resolve detrusor hyperreflexia by blocking the parasympathetic nervous transmission.

#### METHODS

Our planned study population comprised patients with spinal cord injury who emptied the bladder by intermittent self-catheterization. Eligible candidates had severe detrusor hyperreflexia and incontinence resistant to anticholinergic medication. The diagnosis of detrusor hyperreflexia was made by urodynamics. Incontinence was defined as any episode of involuntary voiding between 2 catheterizations. All eligible patients provided informed consent before starting the treatment program and local ethical committees provided full approval of the project. Patients with myasthenia gravis or serious concomitant illness and pregnant or breast feeding women were excluded from analysis. We performed this prospective nonrandomized study on select patients at 2 clinics.

Pretreatment evaluation included a history, serum chemistry and urine cytobacteriology studies, ultrasound of the upper urinary tract and complete urodynamics. None of our patients had any evidence of upper urinary tract damage. Serum chemistry findings were normal in all and none had a urinary tract infection before urodynamics and cystoscopy.

With the patient supine and the pelvis tilted to 15 degrees video urodynamics were done using number 4 radio-opaque microtransducers to determine vesical and urethral pressure. We confirmed correct localization of the transducers within the bladder, bladder neck, and membranous and bulbar urethra with respect to the anatomical pelvic landmarks using an image intensifier. The bladder was filled with 24% contrast medium (5 acetylaminomethyl-5-acetylaminomethyl-2,4,6-triiodobenzoic acid) at a maximum rate of 10 ml. per minute via the urethrovessical measurement catheter. Spot 100 mm. films were obtained for correlative analysis among simultaneous pressure measurements at various anatomical locations of the urethrovessical complex.

As recommended by the Urodynamics Society,<sup>21</sup> intra-abdominal pressure was recorded concurrently with urethrovessical pressure to exclude artifacts and calculate true detrusor pressure.

Medication, especially anticholinergics that would interfere with urethrovessical function, were discontinued at least 1 week before the urodynamic assessment. Neuropathic bladder dysfunction due to upper motor neuron lesions and detrusor hyperreflexia were defined according to the standards of the International Continence Society.<sup>21</sup> The urodynamics exclusion criterion was abnormally low bladder compliance associated with organic detrusor muscle changes. Systematic continuous noninvasive recording of the cardiovascular parameters using a photoplethysmograph was done during urodynamic recording in all cases.

During baseline urodynamics and followup special attention was given to reflex volume, maximum detrusor pressure during voiding, detrusor compliance, maximum cystometric bladder capacity, external urethral sphincter pressure and post-void residual urine volume. Reflex volume was defined as the infused volume that induced the first hyperreflexive detrusor contraction during urethrocystometry.<sup>22</sup> To calculate detrusor compliance using the formula, change in volume/change in detrusor pressure, detrusor pressure was measured with the bladder empty and at maximum cystometric bladder capacity.<sup>22</sup> Maximum cystometric bladder capacity corresponded to the volume at which involuntary voiding occurred and/or filling was stopped.<sup>22</sup> In the absence of involuntary voiding bladder filling was stopped at 500 ml. Post-void residual urine volume was defined as the volume catheterized after voiding or at the end of urodynamics.

Botulinum-A toxin was injected under cystoscopic control on an outpatient basis at our urology department. The bladder was filled with 100 ml. normal saline solution. In patients with spinal cord injury above T5 who were prone to autonomic dysreflexia bladder mucosa anesthesia was ensured by instilling 40 ml. 2% lidocaine, which remained in the bladder for 20 minutes. Under visual control through the cystoscope a total of 200 to 300 units of botulinum-A toxin were injected with a custom made 6Fr flexible injection needle at 20 to 30 detrusor muscle sites, sparing the trigone (fig. 1). A dose of 100 units of commercially available botulinum-A toxin preparation was diluted in 10 ml. normal 0.9% saline solution without a preservative and 10 units per ml. were injected per site. A previous titration study in 5 patients starting from 30 units and rising stepwise at 3-month intervals indicated that about 200 to 300 units were likely to be the most effective dose. Continuous cardiovascular monitoring was performed in all patients during cystoscopy.

After completing treatment patients were asked to record a diary of incontinence, diuria and voiding. They were also required to decrease progressively anticholinergic treatment

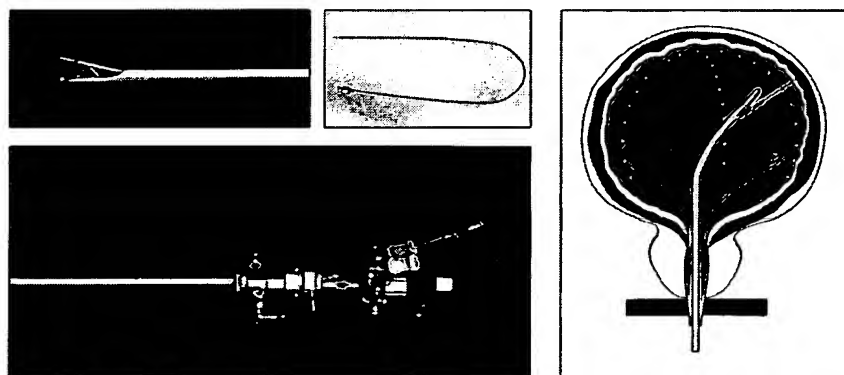


FIG. 1. Mapping of injection sites, and cystoscope and syringe needle

within 1 week after the injections. Clinical and urodynamic followup was planned for 6, 16 and 36 weeks after treatment. Special attention was given to the continence level achieved, actual dose of anticholinergic medication, reflex volume, maximum detrusor pressure during voiding, detrusor compliance, maximum cystometric bladder capacity and patient satisfaction. The latter parameter was estimated on a 3-point scale as 1—not satisfied, 2—satisfied and 3—very satisfied.

Statistical analysis was performed by the paired *t* test with correction for multiple comparisons and significance considered at  $p < 0.016$ . Interim analysis was planned to begin after at least 15 patients entered the study and had a minimum followup of 6 weeks. This analysis assessed the feasibility and tolerance of treatment. Final analysis was planned to begin after all patients were followed at least 36 weeks.

### RESULTS

Between July 1998 and April 1999, 7 women and 14 men 15 to 59 years old (mean age 36.7) with spinal cord injury, severe detrusor hyperreflexia and incontinence entered our study (table 1). Of the 21 patients 18 had paraplegia and 3 tetraplegia. The mean duration of spinal cord injury was 60.2 months (range 2.4 to 350). According to American Spinal Injury Association (ASIA) criteria the spinal cord lesion was complete or ASIA A in 17 cases and incomplete or ASIA B in 4. Complete sensory and motor bladder dysfunction of the upper motor neuron type was present in 17 patients, while in 4 with an upper motor neuron bladder the motor lesion was complete but the sensory lesion was incomplete. Incontinence occurred despite the administration of high doses of anticholinergic drugs (15 to 20 mg. oxybutynin chloride plus 40 to 120 mg. trospium chloride daily) in 16 cases, whereas in 5 severe side effects limited use of the maximum dose. Mean time from initial trauma to baseline urethrocystometry was 61.7 months (range 6 to 350). Median time from baseline urethrocystometry to botulinum-A toxin injections was 3 days.

Toxin administration was uneventful and the whole procedure required no more than 30 minutes. None of the patients had macroscopic hematuria and all were discharged home after cystoscopy. Pre-instillation of lidocaine was an effective means of avoiding autonomic dysreflexia. To date all patients have undergone complete examination 6 weeks after the injections, and 11 at 16 and 36 weeks. We report our interim results.

TABLE 1. Clinical data

Pt.—Age No. (yrs.)	Neurological Level	Upper Motor Neuron Bladder Dysfunction
1—34	T9	Complete
2—25	T12	Complete
3—27	T12, L1	Complete
4—15	C7	Complete
5—33	T11	Complete
6—23	T6	Complete
7—23	T3	Complete
8—39	T12	Complete
9—40	C6	Incomplete
10—26	T5	Complete
11—19	T10	Complete
12—43	T12, L1	Incomplete
13—43	T11, T12	Complete
14—37	T6, T7	Complete
15—32	C6, C7	Incomplete
16—59	T4, T5	Complete
17—54	T4	Complete
18—41	T6, T7	Complete
19—52	T6, T7	Complete
20—57	L3	Incomplete
21—48	T6	Complete

All patients were incontinent and voided by clean intermittent catheterization.

At the 6-week followup (mean 5.7, range 15 to 70 days) 17 of the 19 followed patients were completely continent. Of these patients 10 decreased by 20% to 50% (mean 30%) the amount of anticholinergic medication needed before treatment, while 7 definitively withdrew from medication. These patients were very satisfied with the results (3 points on the score scale). Only 2 of the 19 patients had no more than moderate improvement and remained incontinent after the injections. Interestingly these patients received only 200 units of botulinum-A toxin.

Urodynamic evaluation in all 19 cases revealed significant increases in mean reflex volume plus or minus standard deviation and maximum cystometric bladder capacity from  $215.8 \pm 90.4$  ml. to  $415.7 \pm 211.1$  ( $p < 0.016$ ) and  $296.3 \pm 145.2$  to  $480.5 \pm 134.1$  ( $p < 0.016$ ), respectively. There was a significant increase in mean post-void residual urine volume before and after treatment from  $261.8 \pm 241.3$  ml. to  $490.5 \pm 204.8$  (fig. 2 and table 2). There was also a significant decrease in mean maximum detrusor voiding pressure from  $65.6 \pm 29.2$  cm. water to  $35 \pm 32.1$  ( $p < 0.016$ ) (fig. 3 and table 2). Except for the 2 patients who remained incontinent after treatment none treated successfully voided during the urodynamic examination. Accordingly bladder filling was stopped as soon as the increase in detrusor pressure was constant and at a maximum (fig. 4). This value was then compared with maximum detrusor voiding pressure before treatment. Posttreatment mean detrusor compliance increased markedly from  $32.6 \pm 22.0$  ml./cm. water to  $62.1 \pm 96.6$  but this change was not significant (fig. 3 and table 2). Improvement in urodynamic parameters was even more marked when only the 17 improved cases were considered. In these cases mean reflex volume and mean maximum cystometric bladder capacity increased from  $213.6 \pm 95.3$  ml. to  $433.4 \pm 216.7$  and  $293.2 \pm 148.5$  to  $495.6 \pm 129.9$  ( $p < 0.016$ ), respectively. Mean maximum detrusor pressure during uninhibited detrusor contractions decreased from  $65.1 \pm 27.4$  cm. water (with voiding) before to  $28.8 \pm 20.6$  (without voiding) after treatment, respectively ( $p < 0.016$ ). Mean post-void residual urine volume after and without voiding increased from  $263.5 \pm 247.2$  ml. before to  $519.1 \pm 184.6$  after treatment, respectively. Mean detrusor compliance increased from  $34.6 \pm 22.4$  ml./cm. water to  $68 \pm 100.8$  but this change was not significant, as in the former group.

Overall followup in 11 patients at 16 (mean 16.2, range 11.8 to 27) and 36 (mean 34.5, range 26 to 44) weeks showed ongoing improvement in bladder function. Complete continence persisted in 7 cases, whereas in 4 minor episodes of incontinence were associated with bladder infection. Except for post-void residual urine volume all urodynamic parameters remained statistically improved (figs. 2 and 3, and table 2). At the 36-week followup mean reflex volume was  $319.6 \pm$

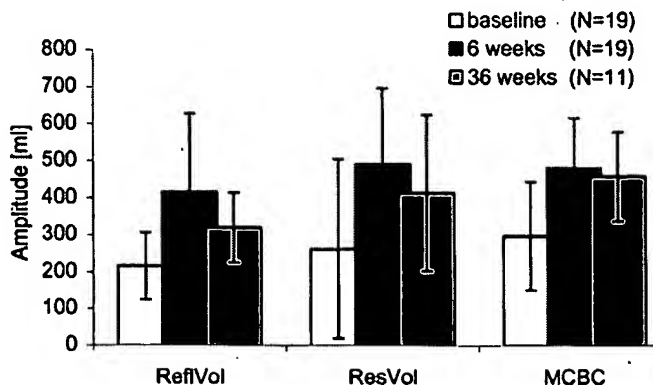


FIG. 2. Mean urodynamic parameters at baseline, and at 6 and 36-week followups. Vertical bars indicate SD. *Refl*, reflex. *Vol*, volume. *Res*, post-void residual urine. *MCBC*, maximum cystometric bladder capacity.

TABLE 2. Urodynamic parameters at baseline and followup

	No. Pts.	Mean Reflex Vol. $\pm$ SD (ml.)	Mean Post-Void Residual Urine Vol. $\pm$ SD (ml.)	Mean Max. Cystometric Bladder Capacity $\pm$ SD (ml.)	Mean Compliance $\pm$ SD (ml./cm. water)	Mean Max. Detrusor Pressure $\pm$ SD (cm. water)
Baseline	19	215.8 $\pm$ 90.4	261.8 $\pm$ 241.3	296.3 $\pm$ 145.2	32.6 $\pm$ 22	65.6 $\pm$ 29.2
Followup (wks.):						
6	19	415.7 $\pm$ 211.1	490.5 $\pm$ 204.8	480.5 $\pm$ 134.1	62.1 $\pm$ 96.6	35 $\pm$ 32.1
36	11	319.6 $\pm$ 93.1	412.5 $\pm$ 209.9	457.5 $\pm$ 120.2	50.2 $\pm$ 34.8	36.5 $\pm$ 15.4

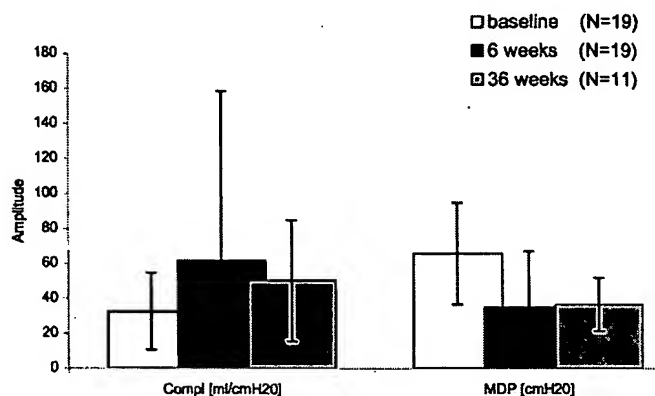


FIG. 3. Mean urodynamic parameters at baseline, and at 6 and 36-week followups. Vertical bars indicate SD. Compl, compliance. MCBC, maximum cystometric bladder capacity.

93.1 ml. and mean maximum cystometric bladder capacity was 457.5  $\pm$  120.2 ( $p < 0.016$ ). Mean maximum detrusor pressure during uninhibited detrusor contractions without voiding decreased to 36.5  $\pm$  15.4 cm. water ( $p < 0.016$ ). Mean post-void residual volume without voiding increased to 412.5  $\pm$  209.9 ml. after treatment. Mean detrusor compliance increased to 50.2  $\pm$  34.8 ml./cm. water but this change was not significant, as in the former group. None of the patients followed at 36 weeks needed repeat botulinum-A toxin injections due to recurrent incontinence.

No side effects were observed at any time, particularly no dysphagia, diplopia or paresis of the remote musculature, and there was no morbidity. Moreover, in the 3 patients with tetraplegia autonomic dysreflexia associated with detrusor hyperreflexia that manifested as a hypertensive crisis during voiding disappeared after treatment.

#### DISCUSSION

To our knowledge our study is the first in humans to show that botulinum-A toxin injections into the detrusor muscle represent an efficient way of releasing detrusor hyperreflexia in spinal cord injured patients. Symptomatic therapeutic chemical denervation was pioneered by Scott.<sup>23</sup> In the early 1980s the Food and Drug Administration approved the therapeutic use of botulinum toxin for strabismus and dystonia, and in 1991 the National Institutes of Health released consensus statements confirming the therapeutic efficacy of botulinum-A toxin for various clinical conditions, including dystonia, strabismus, torticollis and spasticity.<sup>24-27</sup> Botulinum-A toxin is a selective blocker of acetylcholine release from nerve endings and accordingly blocks neural transmission.<sup>28</sup> Botulinum-A toxin binds tightly and rapidly to the intramuscular nerve terminals and causes a prolonged local effect when injected directly into muscle.<sup>29,30</sup> Changes in botulinum treated muscle are consistent with the effects of denervation.<sup>31</sup>

The early study of Dickson and Shevsky initially established that parasympathetic nerve system action may be blocked by botulinum toxin.<sup>32</sup> There has been increasing consensus on the efficiency of botulinum-A toxin for treating autonomic parasympathetic disorders, such as achalasia and

hyperhidrosis.<sup>17-20</sup> Carpenter described a marked loss of contraction in a rat bladder after acute botulin poisoning with a concomitant decrease in acetylcholine release at motor nerve stimulation.<sup>33</sup> However, to our knowledge the effect of injecting botulinum into the human detrusor muscle tract has not been evaluated previously.

The results of our interim analysis strongly imply that injections of botulinum-A toxin into the detrusor muscle suppress bladder overactivity and increase bladder filling. Our patients had a marked increase in cystometric and maximum bladder capacity as well as decreased voiding pressure after treatment. All but 2 patients became continent again and all markedly decreased or withdrew completely from anticholinergic medication. The lack of significant improvement in mean bladder compliance may be explained by the fact that this parameter was within the normal range before treatment. In fact, this criterion was important for selecting patients for therapy. A serious decrease in bladder compliance due to organic detrusor muscle changes or fibrosis does not respond to any conservative treatment. In these cases radical surgery should be considered, such as autoaugmentation, enterocystoplasty or an ileal conduit.

The dose of botulinum-A toxin that we administered was based on a previous titration study. Starting from 30 units the dose was increased stepwise until it was believed that 200 to 300 units were likely to be most effective for completely blocking acetylcholine release at the detrusor level. Since our 2 patients who failed to achieve complete continence after botulinum-A toxin injections received only 200 units, we think that 300 units may be the optimal dose for detrusor hyperreflexia. A higher dose should be avoided due to an increased risk of immunogenicity.<sup>24</sup> Tight binding of the toxin to the local intramuscular nerve terminals prevents passage into the circulatory system and systemic side effects,<sup>29,30</sup> which we never observed in our study.

The decision not to inject the trigone was based on certain major considerations. No injections were made near the osmium to avoid any damage to the upper urinary tract. The submucosal nerve plexus, which is thought to be sensory in nature, is particularly prominent in the trigone.<sup>34</sup> Introducing a syringe needle in this area causes a risk of impairing sensory nerve endings. Also, trigonal innervation is more complex than bladder dome innervation. The superficial and deep trigone appears to be innervated by adrenergic, cholinergic and nonadrenergic noncholinergic excitatory pathways.<sup>35</sup> Therefore, the effect of botulinum-A toxin, which selectively blocks the release of acetylcholine, would have been more difficult to analyze.

The efficacy of botulinum-A toxin injections into the external urethral sphincter for treating neurogenic detrusor-sphincter dyssynergia and improving voiding has been previously reported.<sup>36</sup> However, in our current study we evaluated another indication of botulinum-A toxin in neurogenic voiding disorder, namely restoring continence by suppressing the voiding reflex. We did not concomitantly inject the toxin into the external urethral sphincter or its vicinity in any case. Accordingly the effect of botulinum toxin on detrusor contractility cannot be explained by any change in external urethral sphincter function and no such change was observed on urodynamics.

The duration of induced detrusor paresis was at least more



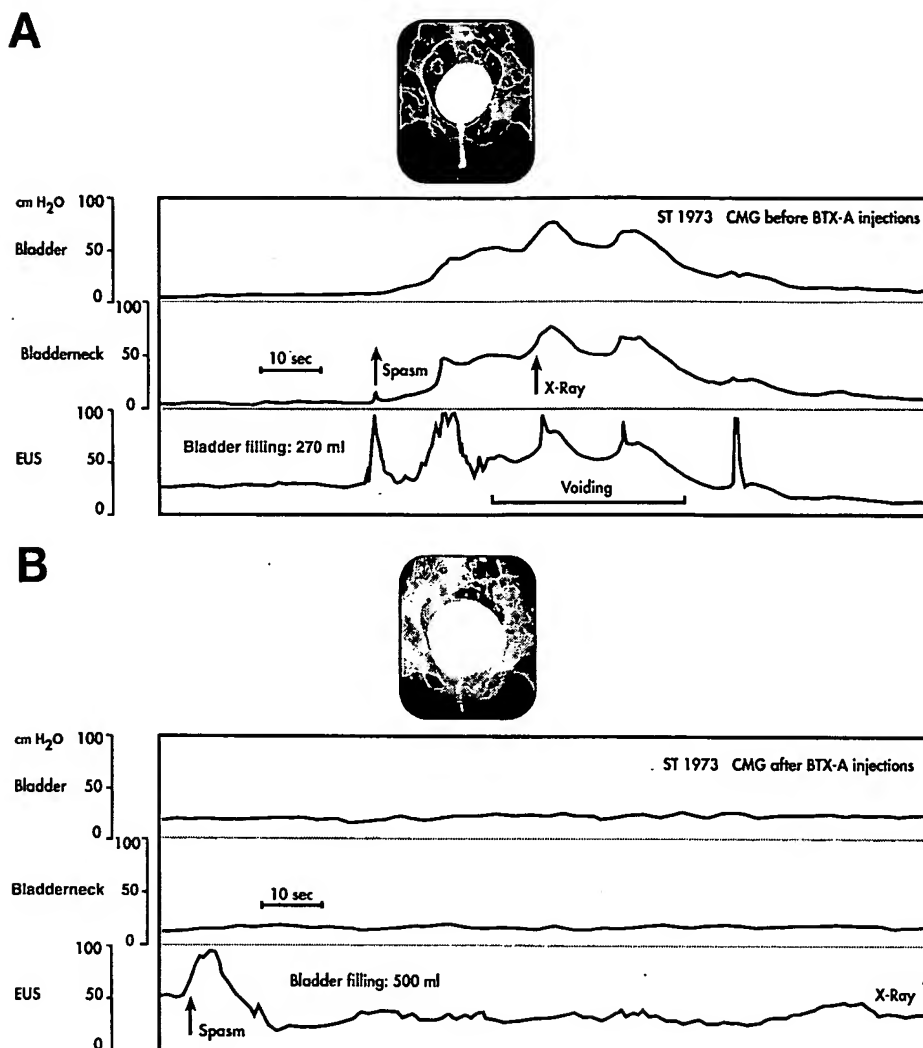


FIG. 4. Urodynamic recordings of patient with complete T5 paraplegia given botulinum-A (BTX-A) injections without anticholinergic medication. A, before injection maximum cystometric capacity was 270 ml. and maximum voiding detrusor pressure 75 cm. water. CMG, cystometrography. EUS, external urinary sphincter. B, after injection maximum cystometric capacity was 500 ml. with no voiding.

than 9 months versus 3 to 4 after a single injection into this muscle to relax the external urethral sphincter.<sup>36</sup> This result strongly implies that smooth and striated muscles react differently to the toxin. Molgo<sup>37</sup> and Holds<sup>38</sup> et al reported axonal sprouting into a striated muscle after botulinum-A toxin injections in animals and humans, which is considered the basis for local re-innervation after acute poisoning. To our knowledge no relevant studies have been done in smooth muscle. Consequently it remains difficult to determine whether the long duration of paralysis induced by the toxin is due to delayed axonal outgrowth when applied to smooth muscle. It also remains to be determined why all of our patients did not withdraw from anticholinergic medication. A hypothesis is that nonadrenergic noncholinergic transmission, which is known to be unaffected by the toxin, has a substantial role in detrusor contraction in these cases.<sup>39</sup>

Our results appear to be encouraging although not all of our patients completely withdrew from anticholinergic drugs. The long-lasting effect of the toxin applied to the detrusor muscle and its lack of side effects make this modality a new therapeutic option for severe neurogenic incontinence. The duration of symptom remission in our cases remains unknown. However, considering the results of treating achalasia with botulinum-A toxin such improvement may be expected to last at least 10 months.<sup>17-20</sup> More studies are

necessary to confirm these preliminary findings and evaluate the long-term effects of botulinum-A injections into the detrusor muscle.

#### CONCLUSIONS

Botulinum-A toxin injections into the detrusor muscle seem to be a safe and reversible conservative treatment for detrusor hyperreflexia and incontinence in spinal cord injured patients. It is longer acting than simple mucosal anesthesia, does not cause the tissue injury associated with a phenol block and avoids the unwanted side effects of intravesical capsaicin instillation.<sup>3,40</sup>

T. Erni assisted with the statistical analysis.

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# A light- and electron-microscopic histopathological study of human bladder mucosa after intravesical resiniferatoxin application

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**Objective** To determine the morphology of bladder mucosa and the integrity of its mucin coat in patients with detrusor hyper-reflexia treated with intravesical resiniferatoxin.

**Patients and methods** Seven patients with detrusor hyper-reflexia were treated intravesically with resiniferatoxin dissolved in 10% ethanol in saline (50 nmol/L solution in two and 100 nmol/L in five). Patients were clinically evaluated by a voiding chart and filling cystometry before and 3 months after each resiniferatoxin application. In addition, they underwent cystoscopy and bladder biopsies at 22–33 months after the first instillation and at 7–23 months after the last one. Tissue samples for light microscopy were fixed in 4% paraformaldehyde, embedded in paraffin and stained with haematoxylin-eosin or periodic acid-Schiff reagent (PAS). Those for electron microscopy were fixed in 5% glutaraldehyde and embedded in resin.

**Results** The resiniferatoxin instillation was not painful. Three months after treatment the mean voiding frequency decreased and five incontinent patients

became continent. The maximum cystometric capacity increased in all patients; at cystoscopy the bladders appeared normal. On light microscopy the urothelium was of normal morphology and stained with PAS in the luminal cells and in the basement membrane. Mononuclear inflammatory cells were occasionally apparent in the lamina propria. On electron microscopy epithelial cells were visible in a thick basal lamina. Superficial cells had the usual irregular contour and contained numerous membrane-coated vesicles. In the lamina propria, unmyelinated axonal profiles with occasional varicosities could be identified.

**Conclusions** Intravesical resiniferatoxin improved urinary frequency, incontinence and bladder capacity in patients with detrusor hyper-reflexia, causing no morphological change in the bladder mucosa. The PAS reactivity of the carbohydrate moieties present in the mucin coat and the basement membrane was unchanged by resiniferatoxin.

**Keywords** resiniferatoxin, bladder, human, histopathology, ultrastructure

## Introduction

Several studies have shown that resiniferatoxin applied intravesically decreases urinary symptoms and increases bladder capacity in patients with detrusor hyper-reflexia [1–3], idiopathic detrusor instability [4] or bladder hypersensitivity [5]. These results are comparable with those previously reported after intravesical capsaicin [6,7]. However, in contrast to that vanilloid, resiniferatoxin instillations were not painful, evoked no episodes of autonomic dysreflexia and were not followed by any transient worsening of urinary symptoms. Taken together, these findings suggest that resiniferatoxin is preferable to capsaicin for intravesical application.

Resiniferatoxin is extracted from the latex of *Euphorbia resinifera*, a cactus-like plant abundant in North Africa. The systematic use by human beings of resiniferatoxin may have been initiated in this region several thousand years ago. According to old texts the dry latex of the euphorbias was used to treat snakebites and other poisonings [8]. Nevertheless, the instillation of resiniferatoxin into the human bladder is still surrounded by some controversy, because of the molecular similarities between resiniferatoxin and tumour-promoting phorbol esters [9]. Apparently, the resemblance is insufficient to give resiniferatoxin typical phorbol ester activity at the cellular level [10]. In addition, resiniferatoxin does not trigger, in the rat skin [11] or urinary bladder [12–14], long-lasting inflammatory reactions, hyperplastic responses or tumour formation, as seen in mouse

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skin after phorbol ester application [15–17]. Although reassuring, these data are insufficient to preclude a careful morphological study of all human tissues exposed to resiniferatoxin. This is more imperative in patients with detrusor hyper-reflexia who are more susceptible to spontaneous urothelial carcinomas than are normal subjects [18,19]. Any histological evaluation should also include a study of the mucin coat and basement membrane of the bladder epithelium, as capsaicin solutions transiently reduce their content of carbohydrate moieties [20]. Bladder mucin was shown to serve as a barrier against bacterial invasion [21], whereas the basement membrane is essential for the anchorage of epithelial cells to the underlying connective tissue [22].

Thus the purpose of the present study was to assess the morphology of bladder mucosa in patients who had undergone repeated intravesical applications of resiniferatoxin. Bladder samples were examined by light and electron microscopy. In addition, by using specific histochemical staining, the effect of resiniferatoxin on the bladder mucin coat and basement membrane was also studied; preliminary data were presented as an abstract [23].

### Patients and methods

Five men and two women (aged 27–47 years) with detrusor hyper-reflexia caused by multiple sclerosis

(three), spinal cord injury (three) and extradural abscess (one) were treated with intravesical resiniferatoxin because they had refractory frequency and urge incontinence (Table 1). Patients completed a voiding chart in which daily micturitions (six patients) or intermittent bladder catheterizations (one) and episodes of incontinence (five) were recorded for at least three consecutive days (Table 1). After a clinical evaluation all patients were screened by haematological and biochemical blood tests, microbiological urinary investigation and an ultrasonographic or radiological evaluation of the urinary system. The maximum cystometric capacity (MCC, Table 1) was measured using a urodynamic system (Dantec, Denmark) with a two-way 8 F catheter inserted in the urethra for the infusion of saline at 50 mL/min and the simultaneous recording of bladder pressure.

Resiniferatoxin (generously donated by Afferon Corporation, USA) was dissolved in 10% ethanol in saline. Each treatment consisted of instillation for 30 min of 100 mL of a 50 nmol/L (in two patients) or 100 nmol/L resiniferatoxin solution (in five) into the empty bladder through a 20 F Foley catheter (Table 1). Except for patient no. 3, the patients had a repeated instillation with a similar solution after a mean of 14 months, because the clinical improvement from the first instillation was not sustained. All the instillations were administered under close vigilance of blood pressure

Table 1 Details of the seven patients in the study and the effects of resiniferatoxin

Detail	Patient no.						
	1	2	3	4	5	6	7
Sex/age (years)	M/35	M/34	M/30	F/47	F/37	M/37	M/27
Diagnosis	EA	MS	SCI	MS	SCI	MS	SCI
Resiniferatoxin dose (nmol/L)	50	50	100	100	100	100	100
No. of instillations	2	2	2	2	1	2	2
Months from							
1st resiniferatoxin to biopsy	28	33	28	26	23	23	22
2nd resiniferatoxin to biopsy	8	21	13	19	23	7	7
Performance status	WA	WC	WA	W/N	WC	WAb	WA
Daily incontinence episodes							
Before resiniferatoxin	0	0	0–1	0–1	>3	0–1	>2
1st resiniferatoxin	0	0	0	0	0	0	0
2nd resiniferatoxin	0	0	0	0	0	0	0
Frequency (times/day)							
Before resiniferatoxin	17	26	10	19	CISC	8	5
1st resiniferatoxin	12	13	7	11	CISC	7	–
2nd resiniferatoxin	8	9	6	11	CISC	7	5
Maximum cystometric capacity (mL)							
Before resiniferatoxin	309	63	51	209	338	212	65
1st resiniferatoxin	262	636	158	411	425	246	167
2nd resiniferatoxin	328	614	387	330	360	–	400

M, male; F, female; EA, extradural abscess; MS, multiple sclerosis; SCI, spinal cord injury; WA, walk with aids; WC, wheelchair; W/N, walk normally; WAb, walk abnormally.

and heart rate, with no form of bladder anaesthesia, and as an outpatient procedure. Three months after each instillation the patients were re-evaluated by voiding chart and filling cystometry. When indicated, the mean results were compared using a *t*-test for means.

Cystoscopy and bladder biopsies were performed under local anaesthesia (20 mL of 2% lidocaine jelly). The intervals between the first or the second resiniferatoxin instillation and biopsy were 22–33 and 7–23 months, respectively (Table 1). Two fragments of the bladder mucosa were taken from the trigone in each patient. The entire procedure was covered by prophylactic antibiotics and besides some slight haematuria, caused no further complications.

Immediately after removal the biopsy fragments were immersion-fixed, one for 4 h in 4% paraformaldehyde in 0.1 mol/L phosphate buffer (pH 7.4) and the other overnight at 4°C in 5% glutaraldehyde in 0.1 mol/L phosphate buffer (pH 7.4). Samples fixed in paraformaldehyde were then washed in phosphate buffer, embedded in paraffin and sections cut on a microtome at 7 µm. The sections were mounted on glass slides and stained with haematoxylin and eosin or periodic acid-Schiff (PAS, 0.5% periodic acid). Samples fixed in glutaraldehyde were washed in 0.1 mol/L phosphate buffer, postfixed for 1 h in 1% osmium tetroxide in phosphate buffer, dehydrated in graded ethanol and embedded in Epon resin. Ultrathin silver sections were cut on an ultramicrotome, stained with lead citrate and uranyl acetate, and examined in an electron microscope.

## Results

The 13 instillations, whether using 50 or 100 nmol/L resiniferatoxin solutions, induced a sharp rise in detrusor pressure, followed by a series of phasic contractions which began within a few minutes of starting the treatment and persisted throughout the instillation. During the initial minutes of resiniferatoxin administration some patients felt an itching or warm sensation in the lower abdomen. In addition, phasic detrusor contractions were associated with an urge to urinate. None of the patients complained of severe discomfort or overt pain during the instillation, or requested any kind of analgesic medication. The blood pressure and heart rate remained stable during treatments. With the exception of patient no. 5, who used CISC to empty his bladder, patients reported a marked decrease in urinary frequency after resiniferatoxin instillation (Table 1). The mean (SD) frequency before resiniferatoxin was 14 (8)/day and this decreased to 9 (3)/day by 3 months after the first treatment ( $P=0.02$ ) and to 8 (2)/day ( $P=0.05$ ) after the second. In addition, the five incontinent patients became continent (Table 1); this clinical improvement was accompanied by

an increase in bladder capacity (Table 1). The mean (SD) MCC of the patients increased from 178 (120) mL at baseline to 329 (172) mL ( $P=0.04$ ) at 3 months after the first instillation and to 403 (107) mL ( $P=0.002$ ) after the second.

On cystoscopy, none of the patients had any urothelial lesion. The histopathological study showed no differences between the samples obtained from the patients treated with 50 or 100 nmol/L resiniferatoxin, and thus the results are presented together. All the biopsies stained with haematoxylin and eosin showed a normal 4–6 layered epithelium with no areas of denudation (Fig. 1a). The superficial cells were larger than the underlying cells and had a central round nucleus. Inflammatory cell infiltrate in the connective tissue underneath the epithelium was minimal or absent (Fig. 1a). In none of the sections examined was there any form of metaplasia, dysplasia of the epithelium or flat *in situ*, papillary or invasive urothelial carcinoma. The bladder epithelium was uniformly stained with PAS (Fig. 1b); the pink

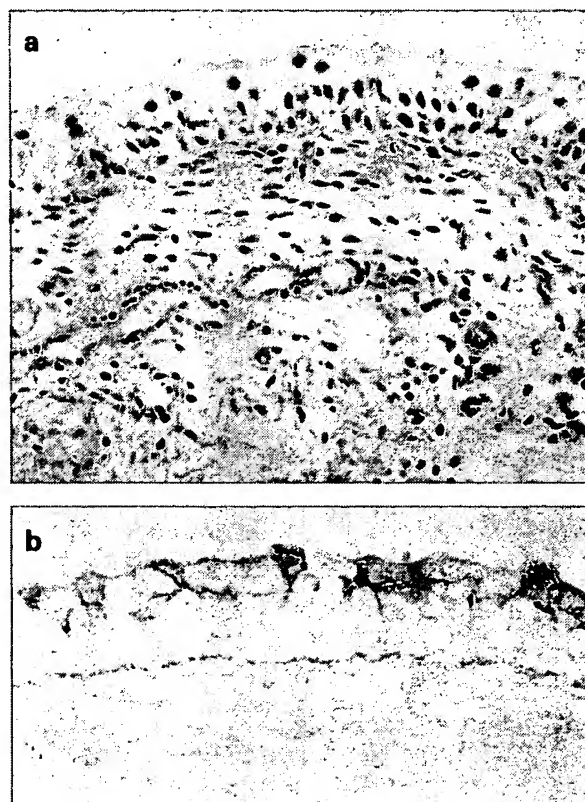


Fig. 1. Light micrographs of the bladder mucosa. a, A bladder biopsy from patient no. 4; the urothelium is normal and there is no inflammatory infiltrate in the lamina propria. Haematoxylin and eosin  $\times 225$ . b, A bladder biopsy from patient no. 1; there is a uniformly pink staining of the mucin coat around superficial urothelial cells and the basement membrane is also PAS-positive. PAS  $\times 225$ .

staining was intense in the contour of the large round cells forming the superficial layer of the epithelium and in the basement membrane.

On electron microscopy the epithelium also appeared normal (Fig. 2a,b). Luminal cells showed the characteristic apical irregular membrane contour, with small indentations alternating with areas appearing stiff and planar (Fig. 2a). Numerous round membrane-coated vesicles were visible in the apical cytoplasm of these cells. The lateral border of the epithelial cells showed the usual profound interdigitations where adhesion processes like gap junctions and desmosomes could be discerned (Fig. 2a). The basal epithelial cells lay over a thick and continuous basal lamina (Fig. 2b). In the lamina propria, unmyelinated axonal profiles of different sizes were frequent (Fig. 2c). A few varicosities full of clear type and dense-core synaptic vesicles were also identified (Fig. 2c).

### Discussion

The full acceptance of intravesical vanilloids for treating patients with detrusor overactivity depends on confirming that these compounds have therapeutic properties and induce no persistent morphological changes in the bladder. Capsaicin, the first vanilloid to be used, showed good clinical efficacy in several studies [6,7], including one placebo-controlled trial [24]. In addition, successive instillations of capsaicin for periods of up to 5 years evoked no morphological changes in the bladder urothelium [25]. Unfortunately, the acute pungency of the product, felt by patients as a strong burning pain in the abdomen, and the risk of severe episodes of autonomic dysreflexia in susceptible patients, impeded the wider use of intravesical capsaicin [6,7]. In contrast, previous clinical trials with intravesical resiniferatoxin showed that this vanilloid was not painful during intravesical application [1–5]. In addition, it decreased the frequency and number of episodes of urinary incontinence, and caused a marked increase in bladder capacity in patients with detrusor overactivity [1–4]. However, histological observations of human

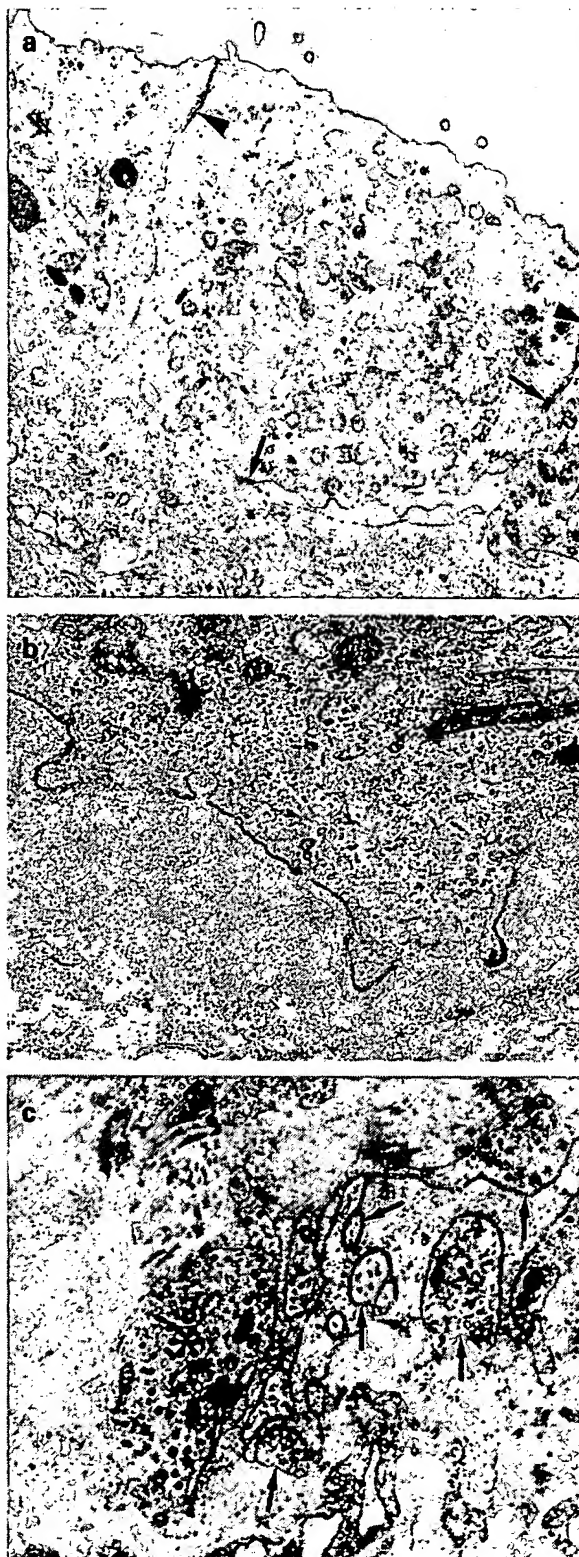


Fig. 2. Electron micrographs of the bladder mucosa. a, This shows the typical angular contour of the luminal border and the numerous membrane-coated vesicles in the apical cytoplasm of the superficial cells of the bladder epithelium. Gap junctions (arrowheads) and desmosomes (arrows) anchor a cell to its neighbours.  $\times 9900$ . b, A continuous basal lamina outlines the inferior border of a basal cell of the bladder epithelium.  $\times 19\,500$ . c, Several unmyelinated axons (arrows) are partially wrapped in a single Schwann cell in the bladder lamina propria. One varicosity (asterisk) is full of small clear and large dense core synaptic vesicles.  $\times 15\,000$ .

bladders exposed to resiniferatoxin have been lacking to date.

Thus the therapeutic effect of intravesical resiniferatoxin, although confirmed by the present study, is not the most important finding. More relevant is the absence of inflammatory reactions, hyperplastic responses or tumour formation in the bladder mucosa of the present patients. Indeed, such changes were shown previously in mouse skin after topical phorbol ester application [15–17] and this was a concern in bladders treated with resiniferatoxin, because of the structural similarities between these molecules [9]. The reason that resiniferatoxin does not mimic phorbol ester activity should be ascribed to its molecular arrangement at C20 that impedes protein kinase C activation in the tissues [26]. Phorbol esters have a free OH radical at this position, whereas resiniferatoxin is esterified with a homovanillic ring [9,27]. Thus, to activate protein kinase C, resiniferatoxin must lose its homovanillic ring, which yields resiniferol-orthophenylacetate as the final product [9]. However, this metabolic step is negligible in the bladder, as the amounts of resiniferol-orthophenylacetate detected after intravesical application of high doses of resiniferatoxin in experimental animals were minimal or undetectable (Afferon Corporation, unpublished data).

Previous studies in the rat showed that the bladder mucin coat loses carbohydrate moieties, and becomes thinner and patch-like during the first 24 h after capsaicin instillation [20]. Because of the time course of the present study it was impossible to confirm or exclude whether resiniferatoxin induced a similar transient dissolution of the human mucin coat. However, the results indicated that resiniferatoxin induced no permanent change in this layer, as the PAS staining of the bladder samples was normal. In addition, the presumed protective function of the mucin coat against bacterial invasion [21] also seemed to remain intact in the present patients; none developed severe cystitis on any occasion.

The basement membrane, like the mucin coat, is rich in carbohydrate moieties [22]. Thus, the positive PAS reaction in the basement membrane of the present bladder samples should be taken as evidence that resiniferatoxin does not change the carbohydrate composition. In addition, electron microscopy showed that the basement membrane formed a thick and continuous band underlining the basal cells of the urothelium. Both findings, together with the absence of denuded bladder areas at cystoscopy, suggest that anchorage of the epithelial cells to the underlying connective tissue is not disturbed by resiniferatoxin.

Finally, electron microscopy showed numerous intact unmyelinated nerve profiles in the urothelial lamina propria. As we did not assess samples obtained before administering resiniferatoxin, this finding cannot exclude

the possibility that resiniferatoxin may have decreased the number of unmyelinated bladder nerve fibres. This aspect of resiniferatoxin action should be considered, as this vanilloid, like capsaicin, induces a massive inflow of calcium into the neurones that may eventually cause their degeneration [6,9,28]. Moreover, previous studies showed that in the bladder of patients who had some clinical improvement from intravesical capsaicin, there was a reduction in the number of unmyelinated axons [7] and a marked loss of nerve fibres immunoreactive to protein gene product 9.5 [29]. However, in a recent ultrastructural study of the bladder of adult rats exposed to topical resiniferatoxin, unmyelinated nerve profiles did not degenerate, despite a transient loss of immunoreactivity to neuropeptides like substance P or calcitonin gene-related peptide [14]. Therefore, this issue should be re-addressed in future work by counting nerve fibres in bladder samples collected from patients before and after resiniferatoxin administration. As resiniferatoxin may decrease the synthesis of substance P, calcitonin gene-related peptide and other neuronal proteins [30], therefore preventing the identification of nerve fibres by standard immunoreactions, it may be worth including electron microscopic techniques in future studies.

In conclusion, this is the first histopathological study showing that the intravesical application of resiniferatoxin in patients with detrusor hyper-reflexia causes no persistent morphological changes in bladder mucosa. This finding reinforces the feasibility of using resiniferatoxin to treat several voiding disturbances and should contribute to the development of new clinical trials designed to compare intravesical resiniferatoxin with other substances currently used to treat detrusor hyper-reflexia. However, these results do not preclude further observations at longer follow-up intervals, as the tumorigenic activity of some substances may not become apparent after several decades of continuous contact with human tissues.

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Abbreviations: MCC, maximum cystometric capacity;

PAS, periodic acid-Schiff.